

(57) Abstract: Hydantoin derivatives of Formula (1) that are useful in the inhibition of metalloproteinases and in particular in the inhibition of TNF- α Converting Enzyme (TACE).

HYDANTOINDERIVATE UND DEREN VERWENDUNG ALS TACE INHIBITOREN

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well
5 as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes and are particularly effective as inhibitors of TNF- α (Tumour Necrosis Factor- α) production. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations
10 these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMP) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14,
15 MMP15, MMP16, MMP17); the reprotolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF- α converting enzymes (ADAM10 and TACE); the ADAM-TS family (for example ADAM-TS1 and ADAM-TS4); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as the endothelin converting enzyme family and the angiotensin
20 converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin.
25 Metalloproteinases are also believed to be important in the processing, or secretion, of biologically important cell mediators, such as tumour necrosis factor- α (TNF- α); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

30 Metalloproteinases have been associated with many disease conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these disease conditions, for example: various inflammatory and allergic diseases such as, inflammation of

the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema and dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis.

A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting TACE. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

TACE (also known as ADAM17) which has been isolated and cloned [R.A. Black *et al.* (1997) *Nature* 385:729-733; M.L. Moss *et al.* (1997) *Nature* 385:733-736] is a member of the adamalysin family of metalloproteins. TACE has been shown to be responsible for the cleavage of pro-TNF- α , a 26kDa membrane bound protein to release 17kDa biologically active soluble TNF- α . [Schlondorff *et al.* (2000) *Biochem. J.* 347: 131-138]. TACE mRNA is found in most tissues, however TNF- α is produced primarily by activated monocytes, macrophages and T lymphocytes. TNF- α has been implicated in a wide range of pro-inflammatory biological processes including induction of adhesion molecules and chemokines to promote cell trafficking, induction of matrix destroying enzymes, activation of fibroblasts to produce prostaglandins and activation of the immune system [Aggarwal *et al* (1996) *Eur. Cytokine Netw.* 7: 93-124]. Clinical use of the anti-TNF- α biologicals has shown TNF- α to play an important role in a range of inflammatory diseases including rheumatoid arthritis, Crohn's disease and psoriasis [Onrust *et al* (1998) *Biodrugs* 10: 397-422, Jarvis *et al* (1999) *Drugs* 57:945-964]. TACE activity has also been implicated in the shedding of other membrane bound proteins including TGF α , p75 & p55 TNF receptors, L-selectin and amyloid precursor protein [Black (2002) *Int. J. Biochem. Cell Biol.* 34: 1-5]. The biology of TACE

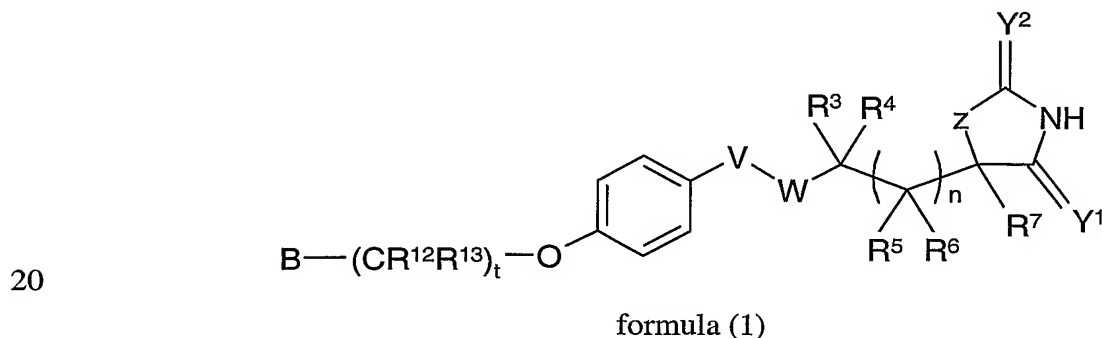
inhibition has recently been reviewed and shows TACE to have a central role in TNF- α production and selective TACE inhibitors to have equal, and possibly greater, efficacy in the collagen induced arthritis model of RA than strategies that directly neutralise TNF- α [Newton et al (2001) Ann. Rheum. Dis. 60: iii25-iii32].

- 5 A TACE inhibitor might therefore be expected to show efficacy in all disease where TNF- α has been implicated including, but not limited to, inflammatory diseases including rheumatoid arthritis and psoriasis, autoimmune diseases, allergic/atopic diseases, transplant rejection and graft versus host disease, cardiovascular disease, reperfusion injury, malignancy and other proliferative diseases. A TACE inhibitor might also be useful in the treatment of
- 10 respiratory disorders such as asthma and chronic obstructive pulmonary diseases (referred to herein as COPD).

TACE inhibitors are known in the art. WO 02/096426 describes hydantoin derivatives which are useful as inhibitors of matrix metalloproteinases, TACE, aggrecanase, or a combination thereof.

- 15 We are able to provide further compounds that have metalloproteinase inhibitory activity, and are in particular inhibitors of TACE (ADAM17).

The present invention provides a compound of formula (1), a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



wherein:

Y^1 and Y^2 are independently O or S;

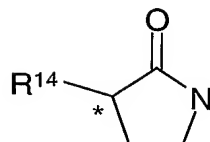
z is NR^8 , O or S;

- 25 n is 0 or 1;

W is NR^1 , CR^1R^2 or a bond;

V is $C(=O)$, $NR^{15}C(=O)$, $NR^{15}SO_2$, SO_2 or a group of formula (A):

-4-



formula (A)

where the group of formula (A) is bonded through nitrogen to W of formula (1) and through

5 carbon * to phenyl of formula (1);

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C₁₋₄alkyl (optionally substituted by R⁹ or one or more halo),

10 C₂₋₄alkenyl (optionally substituted by halo or R⁹), C₂₋₄alkynyl (optionally substituted by halo or R⁹), C₃₋₆cycloalkyl (optionally substituted by R⁹ or one or more halo), C₅₋₆cycloalkenyl

(optionally substituted by halo or R⁹), aryl (optionally substituted by halo or C₁₋₄alkyl),

heteroaryl (optionally substituted by halo or C₁₋₄alkyl), heterocyclyl (optionally substituted by C₁₋₄alkyl), -SR¹¹, -SOR¹¹, -SO₂R¹¹, -SO₂NR⁹R¹⁰, -NR⁹SO₂R¹¹, -NHCONR⁹R¹⁰, -OR⁹,

15 -NR⁹R¹⁰, -CONR⁹R¹⁰ and -NR⁹COR¹⁰; or B is C₂₋₄alkenyl or C₂₋₄alkynyl, each being

optionally substituted by a group selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, -CONHR⁹, -CONR⁹R¹⁰, -SO₂R¹¹, -SO₂NR⁹R¹⁰, -NR⁹SO₂R¹¹, C₁₋₄alkyl and C₁₋₄alkoxy; with the provisos that:

20 when V is a group of formula (A), C(=O), NR¹⁵C(=O) or NR¹⁵SO₂; or when V is SO₂ and n is

1 and W is NR¹, CR¹R² or a bond; or when V is SO₂ and n is 0 and W is CR¹R²; then B is a

group selected from aryl, heteroaryl and heterocyclyl where each group is optionally

substituted by one or more groups independently selected from nitro, trifluoromethyl,

trifluoromethoxy, halo, cyano, C₁₋₄alkyl (optionally substituted by R⁹ or one or more halo),

25 C₂₋₄alkenyl (optionally substituted by halo or R⁹), C₂₋₄alkynyl (optionally substituted by halo or R⁹), C₃₋₆cycloalkyl (optionally substituted by R⁹ or one or more halo), C₅₋₆cycloalkenyl

(optionally substituted by halo or R⁹), aryl (optionally substituted by halo or C₁₋₄alkyl),

heteroaryl (optionally substituted by halo or C₁₋₄alkyl), heterocyclyl (optionally substituted by

C₁₋₄alkyl), -SR¹¹, -SOR¹¹, -SO₂R¹¹, -SO₂NR⁹R¹⁰, -NR⁹SO₂R¹¹, -NHCONR⁹R¹⁰, -OR⁹,

-5-

- $-\text{NR}^9\text{R}^{10}$, $-\text{CONR}^9\text{R}^{10}$ and $-\text{NR}^9\text{COR}^{10}$; or B is C_{2-4} alkenyl or C_{2-4} alkynyl, each being optionally substituted by a group selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-\text{CONHR}^9$, $-\text{CONR}^9\text{R}^{10}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_2\text{NR}^9\text{R}^{10}$,
5 $-\text{NR}^9\text{SO}_2\text{R}^{11}$, C_{1-4} alkyl and C_{1-4} alkoxy; and
when V is SO_2 and n is 0 and W is NR^1 or a bond; then B is a group selected from bicyclic aryl, bicyclic heteroaryl and bicyclic heterocyclyl, where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4} alkyl (optionally substituted by R^9 or one or more halo), C_{2-4} alkenyl
10 (optionally substituted by halo or R^9), C_{2-4} alkynyl (optionally substituted by halo or R^9), C_{3-6} cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6} cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4} alkyl), heteroaryl (optionally substituted by halo or C_{1-4} alkyl), heterocyclyl (optionally substituted by C_{1-4} alkyl), $-\text{SR}^{11}$, $-\text{SOR}^{11}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_2\text{NR}^9\text{R}^{10}$, $-\text{NR}^9\text{SO}_2\text{R}^{11}$, $-\text{NHCONR}^9\text{R}^{10}$, $-\text{OR}^9$, $-\text{NR}^9\text{R}^{10}$,
15 $-\text{CONR}^9\text{R}^{10}$ and $-\text{NR}^9\text{COR}^{10}$; or B is C_{2-4} alkenyl or C_{2-4} alkynyl, each being optionally substituted by a group selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-\text{CONHR}^9$, $-\text{CONR}^9\text{R}^{10}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_2\text{NR}^9\text{R}^{10}$, $-\text{NR}^9\text{SO}_2\text{R}^{11}$, C_{1-4} alkyl and C_{1-4} alkoxy;
20 R^1 and R^2 are independently hydrogen or a group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl and C_{5-6} cycloalkenyl where the group may be optionally substituted by halo, cyano, nitro, hydroxy or C_{1-4} alkoxy;
 R^3 , R^4 , R^5 and R^6 are independently hydrogen or a group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, aryl, heteroaryl and heterocyclyl where the
25 group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, $-\text{OR}^{18}$, $-\text{SR}^{19}$, $-\text{SOR}^{19}$, $-\text{SO}_2\text{R}^{19}$, $-\text{COR}^{19}$, $-\text{CO}_2\text{R}^{18}$, $-\text{CONR}^{18}\text{R}^{20}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{SO}_2\text{NR}^{18}\text{R}^{20}$ and
30 $-\text{NR}^{16}\text{SO}_2\text{R}^{19}$;
or R^1 and R^3 together with the nitrogen or carbon and carbon to which they are respectively attached form a saturated 3- to 7-membered ring optionally containing 1 or 2 heteroatoms

groups selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon or nitrogen by one or more C₁₋₄alkyl;

or R³ and R⁴ together form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally

5 substituted on carbon or nitrogen by one or more C₁₋₄alkyl;

or R³ and R⁵ together with the carbon atoms to which they are attached form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon or nitrogen by one or more C₁₋₄alkyl;

or R⁵ and R⁶ together form a saturated 3- to 7-membered ring optionally containing a

10 heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon or nitrogen by one or more C₁₋₄alkyl;

R⁷ is hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, heteroalkyl, C₃₋₇cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by halo, C₁₋₄alkyl, C₁₋₄alkoxy, C₃₋₇cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and

15 wherein the group from which R⁷ may be selected is optionally substituted on the group and/or on its optional substituent by one or more substituents independently selected from halo, cyano, C₁₋₄alkyl, nitro, haloC₁₋₄alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC₁₋₄alkyl, C₃₋₇cycloalkyl, heterocyclyl, C₁₋₄alkoxyC₁₋₄alkyl, haloC₁₋₄alkoxyC₁₋₄alkyl, carboxyC₁₋₄alkyl, -OR²¹, -CO₂R²¹, -SR²⁵, -SOR²⁵, -SO₂R²⁵, -NR²¹COR²², -CONR²¹R²² and

20 -NHCONR²¹R²²;

or R³ and R⁷ together with the carbon atoms to which they are each attached and (CR⁵R⁶)_n form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon or nitrogen by one or more C₁₋₄alkyl;

25 R⁸ is selected from hydrogen, C₁₋₆alkyl and haloC₁₋₆alkyl;

R⁹ and R¹⁰ are independently hydrogen, C₁₋₆alkyl or C₃₋₆cycloalkyl;

or R⁹ and R¹⁰ together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

R¹¹ is C₁₋₆alkyl or C₃₋₆cycloalkyl;

30 R¹² and R¹³ are independently selected from hydrogen, C₁₋₆alkyl and C₃₋₆cycloalkyl;

R¹⁴ is hydrogen, -NR²³R²⁴ or C₁₋₄alkyl (optionally substituted by halo, -OR²³ and -NR²³R²⁴);

R¹⁶, R²³ and R²⁴ are independently hydrogen or C₁₋₆alkyl;

-7-

R^{17} is selected from halo, C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{1-6} alkoxy;

R^{18} is hydrogen or a group selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, aryl C_{1-4} alkyl and heteroaryl C_{1-4} alkyl where the group is optionally substituted by one or more halo;

5 R^{19} and R^{25} are independently a group selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, aryl C_{1-4} alkyl and heteroaryl C_{1-4} alkyl where the group is optionally substituted by one or more halo;

R^{20} is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

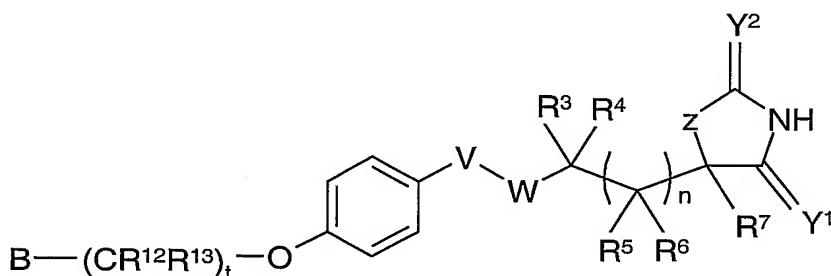
or R^{18} and R^{20} together with the nitrogen to which they are attached form a heterocyclic 4- to

10 7- membered ring;

R^{21} and R^{22} are independently hydrogen, C_{1-4} alkyl, halo C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl and benzoyl.

In particular, the present invention provides a compound of formula (1) or a

15 pharmaceutically acceptable salt thereof wherein:



formula (1)

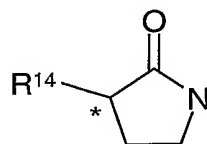
Y^1 and Y^2 are both O;

z is NR^8 , O or S;

20 n is 0 or 1;

W is CR^1R^2 or a bond;

V is a group of formula (A):



formula (A)

where the group of formula (A) is bonded through nitrogen to W of formula (1) and through carbon * to phenyl of formula (1);

t is 0 or 1;

- B** is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C₁₋₄alkyl (optionally substituted by R⁹ or C₁₋₄alkoxy or one or more halo), C₂₋₄alkenyl (optionally substituted by halo or R⁹), C₂₋₄alkynyl (optionally substituted by halo or R⁹), C₃₋₆cycloalkyl (optionally substituted by R⁹ or one or more halo), C₅₋₆cycloalkenyl (optionally substituted by halo or R⁹), aryl (optionally substituted by halo or C₁₋₄alkyl), heteroaryl (optionally substituted by halo or C₁₋₄alkyl), heterocyclyl (optionally substituted by C₁₋₄alkyl), -SR¹¹, -SOR¹¹, -SO₂R¹¹, -SO₂NR⁹R¹⁰, -NR⁹SO₂R¹¹, -NHCONR⁹R¹⁰, -OR⁹, -NR⁹R¹⁰, -CONR⁹R¹⁰ and -NR⁹COR¹⁰; or **B** is C₂₋₄alkenyl or C₂₋₄alkynyl, each being optionally substituted by a group selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl and heterocyclyl which group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, -CONHR⁹, -CONR⁹R¹⁰, -SO₂R¹¹, -SO₂NR⁹R¹⁰, -NR⁹SO₂R¹¹, C₁₋₄alkyl and C₁₋₄alkoxy;
- R**¹ and **R**² are independently hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl and C₅₋₆cycloalkenyl which group may be optionally substituted by halo, cyano, hydroxy or C₁₋₄alkoxy;
- R**³, **R**⁴, **R**⁵ and **R**⁶ are independently hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, aryl, heteroaryl and heterocyclyl which group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₃₋₆cycloalkyl (optionally substituted by one or more R¹⁷), aryl (optionally substituted by one or more R¹⁷), heteroaryl (optionally substituted by one or more R¹⁷), heterocyclyl, -OR¹⁸, -SR¹⁹, -SOR¹⁹, -SO₂R¹⁹, -COR¹⁹, -CO₂R¹⁸, -CONR¹⁸R²⁰, -NR¹⁶COR¹⁸, -SO₂NR¹⁸R²⁰ and -NR¹⁶SO₂R¹⁹; or **R**¹ and **R**³ together with the carbon atoms to which they are attached form a saturated 3- to 7-membered ring optionally containing 1 or 2 heteroatoms groups selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or on nitrogen by -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl or one or more C₁₋₄alkyl;
- or **R**³ and **R**⁴ together with the carbon atom to which they are attached form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and

SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or on nitrogen by -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl or C₁₋₄alkyl;

or **R**³ and **R**⁵ together with the carbon atoms to which they are attached form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and

5 SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or on nitrogen by -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl or C₁₋₄alkyl;

or **R**⁵ and **R**⁶ together with the carbon atom to which they are attached form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and

SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy

10 and/or on nitrogen by -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl or C₁₋₄alkyl;

R⁷ is hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, heteroalkyl, C₃₋₇cycloalkyl, aryl, heteroaryl or heterocyclyl which group is optionally substituted by halo, C₁₋₄alkyl, C₁₋₄alkoxy, C₃₋₇cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and wherein the group from which **R**⁷ may be selected is optionally substituted on the group

15 and/or on its optional substituent by one or more substituents independently selected from halo, cyano, C₁₋₄alkyl, nitro, haloC₁₋₄alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC₁₋₄alkyl, C₃₋₇cycloalkyl, heterocyclyl, C₁₋₄alkoxyC₁₋₄alkyl, haloC₁₋₄alkoxyC₁₋₄alkyl, -COC₁₋₄alkyl, -OR²¹, -NR²¹R²², -CO₂R²¹, -SR²⁵, -SOR²⁵, -SO₂R²⁵, -NR²¹COR²², -CONR²¹R²² and -NHCONR²¹R²²;

20 or **R**³ and **R**⁷ together with the carbon atoms to which they are each attached and (CR⁵R⁶)_n form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or on nitrogen by -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl or C₁₋₄alkyl;

R⁸ is hydrogen or methyl;

25 **R**⁹ and **R**¹⁰ are independently hydrogen, C₁₋₆alkyl or C₃₋₆cycloalkyl;

or **R**⁹ and **R**¹⁰ together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

R¹¹ is C₁₋₆alkyl or C₃₋₆cycloalkyl;

R¹² and **R**¹³ are independently selected from hydrogen, C₁₋₆alkyl and C₃₋₆cycloalkyl;

30 **R**¹⁴ is hydrogen, nitrile, -NR²³R²⁴ or C₁₋₄alkyl (optionally substituted by halo, -OR²³ and -NR²³R²⁴);

R¹⁶, **R**²³ and **R**²⁴ are independently hydrogen or C₁₋₆alkyl;

R^{17} is selected from halo, C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{1-6} alkoxy;

R^{18} is hydrogen or a group selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, aryl C_{1-4} alkyl and heteroaryl C_{1-4} alkyl which group is optionally substituted by one or more halo;

5 R^{19} and R^{25} are independently a group selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-6} cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, aryl C_{1-4} alkyl and heteroaryl C_{1-4} alkyl which group is optionally substituted by one or more halo;

R^{20} is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

or R^{18} and R^{20} together with the nitrogen to which they are attached form a heterocyclic 4- to
10 7- membered ring;

R^{21} and R^{22} are independently hydrogen, C_{1-4} alkyl, halo C_{1-4} alkyl, aryl and aryl C_{1-4} alkyl.

As a further aspect an *in vivo* hydrolysable ester of a compound of formula (1) is provided.

15 It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses metalloproteinases inhibition activity and in particular TACE inhibition activity. The synthesis of optically active forms may be carried out by standard
20 techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Compounds of formula (1) are therefore provided as enantiomers, diastereomers, geometric isomers and atropisomers.

25 Within the present invention it is to be understood that a compound of formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has metalloproteinases inhibition activity and in particular TACE inhibition activity and is not to be limited merely to
30 any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain compounds of formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be

understood that the invention encompasses all such solvated forms which have metalloproteinases inhibition activity and in particular TACE inhibition activity.

It is also to be understood that certain compounds of formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess
5 metalloproteinases inhibition activity and in particular TACE inhibition activity.

The present invention relates to compounds of formula (1) as defined herein as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention
10 may, for example, include acid addition salts of compounds of formula (1) as defined herein which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where compounds of formula (1) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for
15 example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salts for example triethylamine or tris-(2-hydroxyethyl)amine.

The compounds of formula (1) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (1) containing a carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or
20 animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example
25 pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

30 Suitable pharmaceutically acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give

the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include C₁₋₁₀alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C₁₋₁₀alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C₁₋₄)alkylcarbamoyl and *N*-(di-(C₁₋₄)alkylaminoethyl)-*N*-(C₁₋₄)alkylcarbamoyl (to give carbamates); di-(C₁₋₄)alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C₁₋₄)alkylaminomethyl and di-((C₁₋₄)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, R^AC(O)O(C₁₋₆)alkyl-CO-, wherein R^A is for example, benzyloxy-(C₁₋₄)alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C₁₋₄)piperazinyl-(C₁₋₄)alkyl, piperazinyl-(C₁₋₄)alkyl and morpholino-(C₁₋₄)alkyl.

15 In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. For example, "C₁₋₃alkyl" includes methyl, ethyl, propyl and isopropyl, examples of "C₁₋₄alkyl" include the 20 examples of "C₁₋₃alkyl" and butyl and *tert*-butyl and examples of "C₁₋₆alkyl" include the examples of "C₁₋₄alkyl" and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. An analogous convention applies to other generic terms, for example "C₂₋₄alkenyl" includes vinyl, allyl and 1-propenyl and examples of "C₂₋₆alkenyl" include the examples of "C₂₋₄alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3- 25 methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "C₂₋₄alkynyl" includes ethynyl, 1-propynyl, 2-propynyl, 3-butyne and examples of "C₂₋₆alkynyl" include the examples of "C₂₋₄alkynyl" and additionally 2-pentyne, hexynyl and 1-methylpent-2-ynyl. Where examples are given for generic terms, it should be noted that these examples are not limiting.

30 "Cycloalkyl" is a monocyclic, saturated alkyl ring. The term "C₃₋₄cycloalkyl" includes cyclopropyl and cyclobutyl. The term "C₃₋₅cycloalkyl" includes "C₃₋₄cycloalkyl and cyclopentyl. The term "C₃₋₆cycloalkyl" includes "C₃₋₅cycloalkyl", and cyclohexyl. The term

“C₃₋₇cycloalkyl” includes “C₃₋₆cycloalkyl” and additionally cycloheptyl. The term “C₃₋₁₀cycloalkyl” includes “C₃₋₇cycloalkyl” and additionally cyclooctyl, cyclononyl and cyclodecyl.

“Cycloalkenyl” is a monocyclic ring containing 1, 2, 3 or 4 double bonds. Examples of “C₅₋₆cycloalkenyl” are cyclopentenyl, cyclohexenyl and cyclohexadiene and examples of “C₅₋₁₀cycloalkenyl” include the examples of “C₅₋₆cycloalkenyl” and cyclooctatriene.

Unless otherwise specified “aryl” is monocyclic or bicyclic. Examples of “aryl” therefore include phenyl (an example of monocyclic aryl) and naphthyl (an example of bicyclic aryl).

Examples of “arylC₁₋₄alkyl” are benzyl, phenylethyl, naphthylmethyl and naphthylethyl.

Unless otherwise specified “heteroaryl” is a monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen or sulphur may be oxidised. Examples of heteroaryl are pyridyl, imidazolyl, quinolynyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridoimidazolyl, benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indolizynyl, isobenzofuranyl, quinazolinyl, imidazopyridinyl and pyrazolopyridinyl. Preferably heteroaryl is pyridyl, imidazolyl, quinolynyl, pyrimidinyl, thienyl, pyrazolyl, thiazolyl, oxazolyl and isoxazolyl. More preferably heteroaryl is pyridyl, imidazolyl and pyrimidinyl. Examples of “monocyclic heteroaryl” are pyridyl, imidazolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl and pyrazinyl. Examples of “bicyclic heteroaryl” are quinolynyl, quinazolinyl, cinnolynyl, pyridoimidazolyl, benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indolizynyl, isobenzofuranyl, quinazolinyl, imidazopyridinyl and pyrazolopyridinyl. Preferred examples B when B is heteroaryl are those examples of bicyclic heteroaryl.

Examples of “heteroarylC₁₋₄alkyl” are pyridylmethyl, pyridylethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrimidinylbutyl, imidazolylpropyl, imidazolylbutyl, quinolynylpropyl, 1,3,4-triazolylpropyl and oxazolylmethyl.

“Heterocyclyl” is a saturated, unsaturated or partially saturated, monocyclic or bicyclic ring (unless otherwise stated) containing 4 to 12 atoms of which 1, 2, 3 or 4 ring

atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)-; and where unless stated to the contrary a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s); a ring -NH is optionally substituted by acetyl, formyl, methyl or mesyl; and a ring is optionally substituted by one or more halo. Examples and suitable values of the term "heterocyclyl" are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidiny, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, pyranyl, dihydro-2*H*-pyranyl, tetrahydrofuranly, 2,5-dioximidazolidinyl, 2,2-dimethyl-1,3-dioxolanyl and 3,4-dimethylenedioxyphenyl. Preferred values are 3,4-dihydro-2*H*-pyran-5-yl, tetrahydrofuran-2-yl, 2,5-dioximidazolidinyl, 2,2-dimethyl-1,3-dioxolan-2-yl and 3,4-methylenedioxyphenyl. Other values are pyridoimidazolyl, benzimidazolyl, benzofuranly, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indoliziny, isobenzofuranly, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, indolinyl, tetrahydroquinoline, tetrahydroisoquinoline and isoindolinyl. Examples of monocyclic heterocyclyl are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidiny, oxetanyl, morpholinyl, pyranyl, tetrahydrofuranly, 2,5-dioximidazolidinyl and 2,2-dimethyl-1,3-dioxolanyl. Examples of bicyclic heterocyclyl are pyridoimidazolyl, benzimidazolyl, benzofuranly, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indoliziny, isobenzofuranly, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, isoindolinyl. 2,3-methylenedioxyphenyl, and 3,4-methylenedioxyphenyl. Examples of saturated heterocyclyl are piperidinyl, pyrrolidinyl and morpholinyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C₁₋₃alkoxy" and "C₁₋₄alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "C₁₋₆alkoxy" include the examples of "C₁₋₄alkoxy" and additionally pentyloxy, 1-ethylpropoxy and hexyloxy.

"Heteroalkyl" is alkyl containing at least one carbon atom and having at least one carbon atom replaced by a hetero group independently selected from N, O, S, SO, SO₂, (a hetero group being a hetero atom or group of atoms). Examples include -CH₂OCH₃, -CH₂SH and -OC₂H₅.

“HaloC₁₋₄alkyl” is a C₁₋₄alkyl group substituted by one or more halo. Examples of “haloC₁₋₄alkyl” include fluoromethyl, trifluoromethyl, 1-chloroethyl, 2-chloroethyl, 2-bromopropyl, 1-fluoroisopropyl and 4-chlorobutyl. Examples of “haloC₁₋₆alkyl” include the examples of “haloC₁₋₄alkyl” and 1-chloropentyl, 3-chloropentyl and 2-fluorohexyl.

5 Examples of “hydroxyC₁₋₄alkyl” include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl.

Example of “C₁₋₄alkoxyC₁₋₄alkyl” include methoxymethyl, ethoxymethyl, methoxyethyl, methoxypropyl and propoxybutyl.

“HaloC₁₋₄alkoxyC₁₋₄alkyl” is a C₁₋₄alkoxyC₁₋₄alkyl group substituted on C₁₋₄alkoxy by
10 one or more halo. Examples of “haloC₁₋₄alkoxyC₁₋₄alkyl” include 1-(chloromethoxy)ethyl, 2-fluoroethoxymethyl, trifluoromethoxymethyl, 2-(4-bromobutoxy)ethyl and 2-(2-iodoethoxy)ethyl.

Examples of “carboxyC₁₋₄alkyl” include carboxymethyl, 2-carboxyethyl and 2-carboxypropyl.

15 Heterocyclic rings are rings containing 1, 2 or 3 ring atoms selected from nitrogen, oxygen and sulphur. “Heterocyclic 5 to 7-membered” rings are pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl, thiomorpholinyl, thiopyranyl and morpholinyl. “Heterocyclic 4 to 7-membered” rings include the examples of “heterocyclic 5 to 7-membered” and additionally azetidiny.

20 Examples of saturated 3- to 7-membered rings optionally containing 1 or 2 heteroatom groups selected from NH, O, S, SO or SO₂ include cyclopropyl, cyclohexane, cyclopentane, piperidine, pyrrolidine, morpholine, tetrahydrofuran and tetrahydropyran. Examples of saturated 5- to 7-membered rings optionally containing a heteroatom groups selected from NH, O, S, SO or SO₂ include cyclohexane, cyclopentane, piperidine, pyrrolidine,
25 tetrahydrofuran and tetrahydropyran.

Where optional substituents are chosen from “one or more” groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. Preferably “one or more” means “1, 2 or 3” and this is particularly the case when the group or
30 substituent is halo. “One or more” may also mean “1 or 2”.

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 5.09).

Preferred values of z , n , W , t , B , R^3 , R^4 , R^5 , R^6 , R^7 , R^{12} and R^{13} are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined herein.

5 In one aspect of the invention z is NR^8 .

In one aspect of the invention n is 1. In another aspect n is 0.

In one aspect of the invention W is CR^1R^2 . In a further aspect W is a bond.

In one aspect of the invention t is 0. In another aspect t is 1.

In one aspect of the invention, B is a group selected from aryl, heteroaryl and

10 heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkyl (optionally substituted by one or more halo), C_{2-4} alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4} alkenyl or C_{2-4} alkynyl optionally substituted by C_{1-4} alkyl,

C_{3-6} cycloalkyl or heterocyclyl. In another aspect B is a group selected from bicyclic aryl or

15 bicyclic heteroaryl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkyl (optionally substituted by one or more halo), C_{2-4} alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4} alkenyl or C_{2-4} alkynyl optionally substituted by

C_{1-4} alkyl, C_{3-6} cycloalkyl or heterocyclyl. In another aspect, B is phenyl, naphthyl, pyridyl,

20 quinoliny, isoquinoliny, thienopyridyl, 1,8-naphthyridinyl, 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 1,6-naphthyridinyl, thienopyrimidinyl, pyridoimidazolyl,

benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl,

benzisoxazolyl, benzisothiazolyl, indazolyl, indoliziny, isobenzofuranyl, quinazoliny,

imidazopyridinyl, pyrazolopyridinyl, indoliny, tetrahydroquinoliny, tetrahydroisoquinoliny

25 or isoindoliny, where each is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkyl (optionally substituted by one or more fluoro), C_{2-4} alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is vinyl or ethynyl optionally substituted by C_{1-4} alkyl. In another aspect B

is phenyl, naphthyl, pyridyl, quinoliny, isoquinoliny, thieno[2,3-*b*]pyridyl, thieno[3,2-

30 *b*]pyridyl, 1,8-naphthyridinyl, 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 1,6-naphthyridinyl, thieno[2,3-*d*]pyrimidinyl or thieno[3,2-*d*]pyrimidinyl where each is optionally substituted by one or more groups independently selected from trifluoromethyl,

trifluoromethoxy, fluoro, chloro, bromo, methyl, isopropyl, ethynyl, cyano, acetamido, propyloxy, isopropoxy, methoxy, nitro, pyrrolidinylcarbonyl, *N*-propylcarbamoyl, pyrrolidinyl, piperidinyl, isoxazolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrimidinyl and pyridyl; or B is vinyl or ethynyl optionally substituted by methyl or ethyl. In a further aspect B is quinolin-4-yl, naphthyl, 2-methylquinolin-4-yl, 3-methylnaphthyl, 7-methylquinolin-5-yl, 6-methylquinolin-8-yl, 7-methylisoquinolin-5-yl, 6-methylthieno[2,3-*b*]pyridyl, 5-methylthieno[3,2-*b*]pyridyl, 2-methyl-1,8-naphthyridinyl, 2-trifluoromethylquinolin-4-yl, 2-ethynylquinolin-4-yl, 7-chloroquinolin-5-yl, 7-fluoro-2-methylquinolin-4-yl, 2-methyl-*N*-oxoquinolin-4-yl, 3-methylisoquinolin-1-yl, 5-fluoro-2-methylquinolin-4-yl, 2,6-dimethylpyrid-4-yl, 2,5-dimethylpyridin-4-yl, 2,5-dimethylphenyl, 2,5-difluorophenyl, 2,6-difluoro-3-methylphenyl, 2-chloro-6-fluorophenyl, 5-fluoro-2-methylphenyl, 2,6-difluorophenyl, 2,6-dichlorophenyl, 3,5-dimethylphenyl, 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 5-fluoro-2-methylpyridinyl, 1-methylquinolinyl, 7-chloroquinolin-4-yl, 8-chloroquinolin-4-yl, 3-chloro-5-trifluoromethylpyrid-2-yl, 3,5-dichloropyrid-2-yl, 6-chloroquinolin-4-yl, 5-methylthieno[2,3-*d*]pyrimidin-4-yl, 7-methylthieno[3,2-*d*]pyrimidin-4-yl, 8-fluoroquinolin-4-yl, 6-fluoroquinolin-4-yl, 2-methylquinolin-4-yl, 6-chloro-2-methylquinolin-4-yl, 1,6-naphthyridin-4-yl, thieno[3,2-*b*]pyrid-7-yl, 2-chloro-5-fluorophenyl, ethynyl, prop-1-enyl, prop-1-ynyl or but-1-ynyl. In another aspect of the invention B is a group selected from quinolinyl, pyridyl and phenyl where each group is optionally substituted by one or more methyl, trifluoromethyl, trifluoromethoxy, halo or isoxazolyl. In a further aspect B is aryl, heteroaryl or C₂₋₄alkynyl optionally substituted by halo or C₁₋₄alkyl. In another aspect B is 2-methylquinolin-4-yl, 2,5-dimethylphenyl, 2,5-dimethylpyrid-4-yl, phenyl, 3,5-difluorophenyl or prop-1-ynyl. In a further aspect of the invention B is 2-methylquinolin-4-yl, 2,5-dimethylphenyl or 2,5-dimethylpyrid-4-yl. In yet another aspect B is 2-methylquinolin-4-yl or 2,5-dimethylphenyl.

In one aspect of the invention R¹ is hydrogen or methyl.

In one aspect of the invention R² is hydrogen or methyl.

In one aspect of the invention R³ is hydrogen, methyl, ethyl, propyl or phenyl. In another aspect R³ is hydrogen or methyl.

In one aspect of the invention R¹ and R³ together with the carbon atoms to which they are attached form a 2,2-dimethylthiomorpholine, piperidine, pyrrolidine, piperazine, morpholine, cyclopentane or cyclohexane ring.

In one aspect of the invention R^4 is hydrogen or methyl. In another aspect R^4 is hydrogen.

In one aspect of the invention R^3 and R^4 together form a pyrrolidine ring, a piperidine ring, a tetrahydrofuran ring or a tetrahydropyran ring. In another aspect R^3 and R^4 together
5 form a pyrrolidine ring or a tetrahydro-2H-pyran ring.

In one aspect of the invention R^5 is hydrogen or methyl.

In one aspect of the invention R^3 and R^5 together with the carbon atoms to which they are attached form a piperidine ring optionally substituted by methyl.

In one aspect of the invention R^6 is hydrogen or methyl.

10 In one aspect of the invention R^7 is hydrogen or a group selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl or heterocyclyl which group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substituents independently selected from halo, cyano, C_{1-4} alkyl, $-COC_{1-3}$ alkyl, $-SO_2C_{1-3}$ alkyl,
15 $-OR^{21}$, $-NR^{21}R^{22}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$. In another aspect R^7 is hydrogen or a group selected from C_{1-4} alkyl, aryl C_{1-4} alkyl, heteroaryl C_{1-4} alkyl, heterocyclyl C_{1-4} alkyl, aryl, heteroaryl, heterocyclyl and C_{3-5} cycloalkyl which group is optionally substituted by cyano, C_{1-4} alkyl, halo, $-OR^{21}$, $-NR^{21}R^{22}$, $-COC_{1-3}$ alkyl and $-SO_2C_{1-3}$ alkyl. In a further aspect R^7 is hydrogen or a group selected from C_{1-4} alkyl,
20 tetrahydrofuran, tetrahydropyran, pyrrolidinyl, piperidinyl and morpholinyl optionally substituted by methyl, ethyl, methoxy, ethoxy, fluoro, $-COC_{1-3}$ alkyl or $-SO_2C_{1-3}$ alkyl. In a further aspect R^7 is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, *tert*-butyl, isobutyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, aminomethyl, 2-cyanoethyl, phenyl, pyridyl, benzyl, 3-methylbenzyl, phenylethyl, 4-chlorophenylethyl, 4-fluorophenylethyl, phenylpropyl, 4-chlorophenylpropyl, 4-fluorophenylpropyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylethyl, morpholin-4-ylpropyl, pyrimidin-2-ylethyl, pyrimidin-2-ylpropyl, pyrimidin-2-ylbutyl, 5-fluoropyrimidin-2-ylpropyl, imidazol-1-ylpropyl, imidazol-1-ylbutyl, 1,3,4-triazolylpropyl, piperidinyl, carbamoylphenyl, tetrahydro-2H-pyranyl, tetrahydro-2H-pyranylmethyl, pyrid-2-ylmethyl, pyrid-4-ylmethyl, pyrid-3-ylmethyl,
25 piperidin-4-ylmethyl, N-(methylcarbonyl)piperidin-4-yl, N-(*tert*-butoxycarbonyl)piperidin-4-yl, benzyloxyethyl, N-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl, (3,4,4-trimethyl-2,5-dioximidazolidin-1-yl)methyl, methoxymethyl, methoxyethyl and N-benzoyl-N-

phenylaminomethyl. In one aspect R^7 is selected from hydrogen, C_{1-4} alkyl, halo C_{1-4} alkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl and aryl. In another aspect R^7 is hydrogen, methyl, hydroxymethyl, isobutyl or phenyl.

In one aspect of the invention R^3 and R^7 together with the carbon atoms to which they
5 are each attached and $(CR^5R^6)_n$ form a piperidinyl, pyrrolidinyl, piperazine or morpholine ring.

In one aspect of the invention R^8 is hydrogen.

In one aspect of the invention R^9 is hydrogen or methyl.

In one aspect of the invention R^{10} is hydrogen or methyl.

10 In one aspect of the invention R^{11} is methyl.

In one aspect of the invention R^{12} is hydrogen or methyl.

In one aspect of the invention R^{13} is hydrogen or methyl.

In one aspect of the invention R^{14} is hydrogen, $-NR^{23}R^{24}$ or C_{1-4} alkyl (optionally substituted by halo, $-OR^{23}$ and $-NR^{23}R^{24}$. In one aspect R^{14} is hydrogen, methyl or amino.

15 In one aspect of the invention R^{16} is hydrogen or methyl.

In one aspect of the invention R^{17} is selected from fluoro, chloro, methyl or methoxy.

In one aspect of the invention R^{19} is a group selected from C_{1-6} alkyl, aryl and aryl C_{1-4} alkyl where the group is optionally substituted by halo. In another aspect R^{19} is a group selected from methyl, phenyl and benzyl where the group is optionally substituted by
20 chloro. In one aspect R^{19} is methyl.

In one aspect of the invention R^{18} is hydrogen or a group selected from C_{1-6} alkyl, aryl and aryl C_{1-4} alkyl which group is optionally substituted by halo. In another aspect R^{18} is hydrogen or a group selected from methyl, phenyl and benzyl which group is optionally substituted by chloro.

25 In one aspect of the invention R^{20} is hydrogen or methyl.

In one aspect of the invention R^{21} is hydrogen, methyl, ethyl, phenyl or benzyl. In another aspect R^{21} is hydrogen.

In one aspect R^{22} is hydrogen, methyl, ethyl, phenyl or benzyl. In another aspect R^{22} is hydrogen or methyl.

30 In one aspect of the invention R^{23} is hydrogen or methyl.

In one aspect of the invention R^{24} is hydrogen or methyl.

In one aspect of the invention R^{25} is a group selected from C_{1-6} alkyl, aryl and

arylC₁₋₄alkyl which group is optionally substituted by halo. In another aspect R²⁵ is a group selected from methyl, phenyl and benzyl which group is optionally substituted by chloro. In one aspect of the invention R²⁵ is methyl.

5 A preferred class of compound is of formula (1) wherein:

Y¹ and Y² are both O;

z is NR⁸;

n is 0 or 1;

W is CR¹R² or a bond;

10 V is a group of formula (A);

t is 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl,

trifluoromethoxy, halo, C₁₋₄alkyl (optionally substituted by one or more halo), C₂₋₄alkynyl,

15 heteroaryl, -OR⁹, cyano, -NR⁹R¹⁰, -CONR⁹R¹⁰ and -NR⁹COR¹⁰; or B is C₂₋₄alkenyl or C₂₋₄alkynyl optionally substituted by C₁₋₄alkyl, C₃₋₆cycloalkyl or heterocyclyl.

R¹ and R² are independently hydrogen or methyl;

R³ is hydrogen, methyl, ethyl, propyl or phenyl;

R⁴, R⁵, R⁶, R⁹, R¹⁰, R¹², R²³ and R²⁴ are independently hydrogen or methyl;

20 R⁷ is hydrogen or a group selected from C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, heteroaryl or heterocyclyl which group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R⁷ may be selected is optionally substituted on the group and/or on its optional substituent by one or more substituents independently selected from halo, cyano, C₁₋₄alkyl, -COC₁₋₃alkyl, -SO₂C₁₋₃alkyl, -OR²¹, -NR²¹R²², -CO₂R²¹, -

25 NR²¹COR²², -NR²¹CO₂R²² and -CONR²¹R²²;

R⁸ is hydrogen;

R¹⁴ is hydrogen, -NR²³R²⁴ or C₁₋₄alkyl (optionally substituted by halo, -OR²³ or -NR²³R²⁴);

and

R²¹ and R²² are independently hydrogen, methyl, ethyl, phenyl or benzyl.

30

Another preferred class of compounds is of formula (1) wherein:

Y¹ and Y² are both O;

z is NR⁸;

n is 0 or 1;

W is CR¹R² or a bond;

V is a group of formula (A);

5 t is 1;

B is phenyl, naphthyl, pyridyl, quinoliny, isoquinoliny, thienopyridyl, 1,8-naphthyridinyl, 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 1,6-naphthyridinyl, thienopyrimidinyl, pyridoimidazolyl, benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indoliziny, isobenzofuranyl,

10 quinazoliny, imidazopyridinyl, pyrazolopyridinyl, indoliny, tetrahydroquinoliny, tetrahydroisoquinoliny or isoindoliny, where each is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkyl (optionally substituted by one or more fluoro), C₂₋₄alkynyl, heteroaryl, -OR⁹, cyano, -NR⁹R¹⁰, -CONR⁹R¹⁰ and -NR⁹COR¹⁰; or B is vinyl or ethynyl optionally substituted by C₁₋₄alkyl;

15 R¹ and R² are independently hydrogen or methyl;

R³, R⁴, R⁵, R⁶, R⁹, R¹⁰, R¹² and R¹³ are independently hydrogen or methyl; and

R⁷ is hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl or aryl;

R⁸ is hydrogen; and

R¹⁴ is hydrogen, methyl or amino.

20

Another preferred class of compounds is of formula (1) wherein:

Y¹ and Y² are both O;

z is NR⁸;

n is 0 or 1;

25 W is CR¹R² or a bond;

V is a group of formula (A);

t is 1;

B is aryl, heteroaryl or C₁₋₄alkynyl optionally substituted by halo or C₁₋₄alkyl;

R¹ and R² are independently hydrogen or methyl;

30 R³, R⁴, R⁵, R⁶, R¹² and R¹³ are independently hydrogen or methyl; and

R⁷ is hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl or aryl.

R⁸ is hydrogen; and

R^{14} is hydrogen, methyl or amino.

Another preferred class of compounds is of formula (1) wherein:

Y^1 and Y^2 are both O;

5 z is NR^8 ;

n is 0;

W is a bond;

V is a group of formula (A);

t is 1;

10 B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4} alkyl (optionally substituted by one or more halo), C_{2-4} alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4} alkenyl or C_{2-4} alkynyl optionally substituted by C_{1-4} alkyl, C_{3-6} cycloalkyl or heterocyclyl;

15 $R^3, R^4, R^5, R^6, R^9, R^{10}, R^{12}$ and R^{13} are independently hydrogen or methyl; and

R^7 is hydrogen, C_{1-4} alkyl, halo C_{1-4} alkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl or aryl.

R^8 is hydrogen; and

R^{14} is hydrogen, methyl or amino.

20 Another preferred class of compounds is of formula (1) wherein:

Y^1 and Y^2 are both O;

z is NR^8 ;

n is 0;

W is a bond;

25 V is a group of formula (A);

t is 1;

B is aryl, heteroaryl or C_{1-4} alkynyl optionally substituted by halo or C_{1-4} alkyl

R^1 and R^2 are independently hydrogen or methyl;

$R^3, R^4, R^5, R^6, R^{12}$ and R^{13} are independently hydrogen or methyl; and

30 R^7 is hydrogen, C_{1-4} alkyl, halo C_{1-4} alkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl or aryl.

R^8 is hydrogen; and

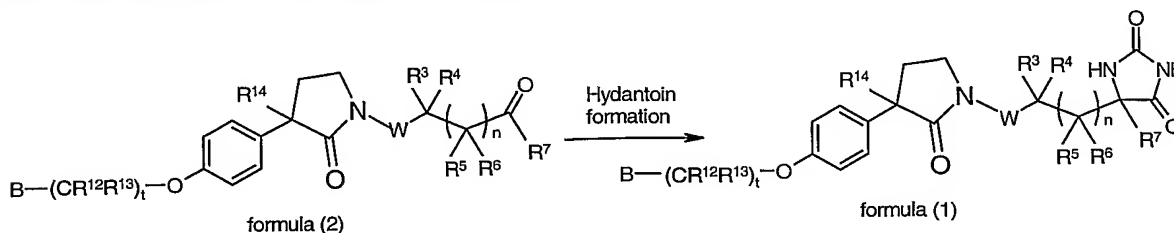
R^{14} is hydrogen, methyl or amino.

In another aspect of the invention, preferred compounds of the invention are any one of:

- (R/S)-5-(1-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}ethyl)imidazolidine-2,4-dione;
- (R/S)-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione;
- 5-methyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione;
- 10 5-{3-amino-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione dihydrochloride;
- 5-[3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-ylmethyl]imidazolidine-2,4-dione;
- 5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}-5-phenylimidazolidine-2,4-dione;
- 15 5-isobutyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione;
- 5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione;
- 5-[(3-{4-[(3,5-difluorobenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione;
- 20 5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]-5-methylimidazolidine-2,4-dione;
- 5-hydroxymethyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}-imidazolidine-2,4-dione;
- 25 5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]-5-methylimidazolidine-2,4-dione;
- 5-[(3-methyl-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione; and
- 5-[(3-amino-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione.
- 30

-24-

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Y^1 and Y^2 are both O, z is NR^8 and R^8 is hydrogen, which comprises converting a ketone or aldehyde of formula (2) into a hydantoin of formula (1);



Scheme 1

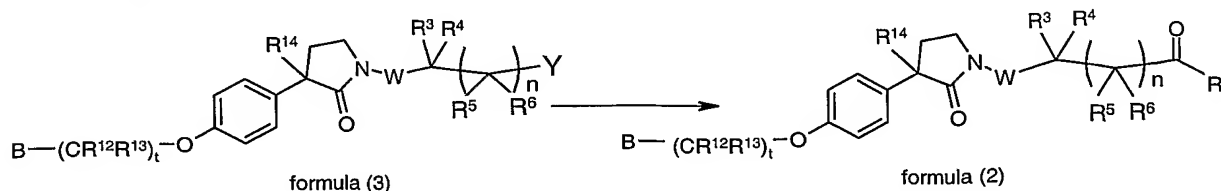
and thereafter if necessary:

- i) converting a compound of formula (1) into another compound of formula (1);
- ii) removing any protecting groups;
- 10 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

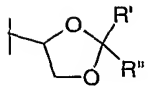
The hydantoin can be prepared by a number of methods for example:

- a) The aldehyde or ketone may be reacted with ammonium carbonate and potassium cyanide in aqueous alcohols using the method of Bucherer and Berge (*Adv. Het. Chem.*, 1985, **38**, 177).
- 15 b) The aldehyde or ketone could be first converted to the cyanohydrin and then further reacted with ammonium carbonate (*Chem. Rev*, 1950, **56**, 403).
- c) The aldehyde or ketone could be converted to the alpha-amino nitrile and then either reacted with ammonium carbonate or aqueous carbon dioxide or potassium cyanate followed by mineral acid (*Chem. Rev*, 1950, **56**, 403).

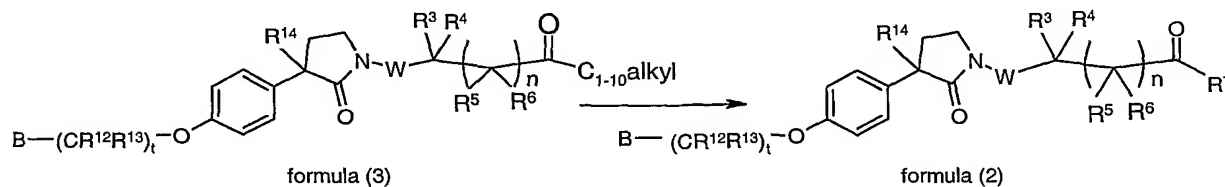
- 20 A process for the preparation of a ketone or aldehyde of formula (2) comprises converting a compound of formula (3) into a ketone or aldehyde of formula (2):



Scheme 2

wherein Y is an ester group such as $-\text{COOC}_{1-10}\text{alkyl}$; a ketal such as  where R' and R'' are $\text{C}_{1-10}\text{alkyl}$; an alcohol group such as $-\text{CHR}^7\text{OH}$; or an alkene group such as $\text{CR}^7=\text{CH}_2$.

a) when Y is an ester group so that scheme 2 illustrates the reaction:

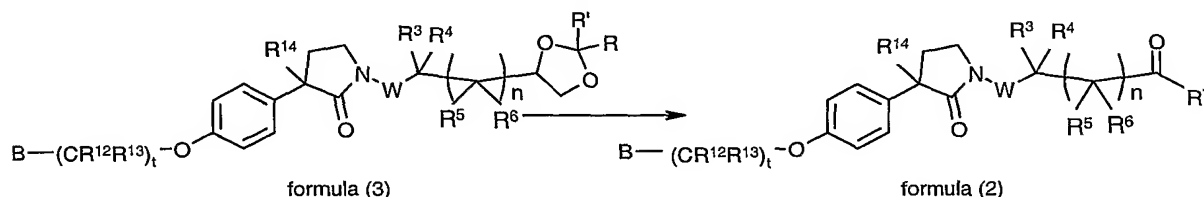


5

Scheme 2a

suitable reagents are Grignard reagents to prepare ketones or diisobutylaluminium hydride in dichloromethane at -78°C under an argon atmosphere to prepare aldehydes.

b) when Y is a ketal so that scheme 2 illustrates the reaction:

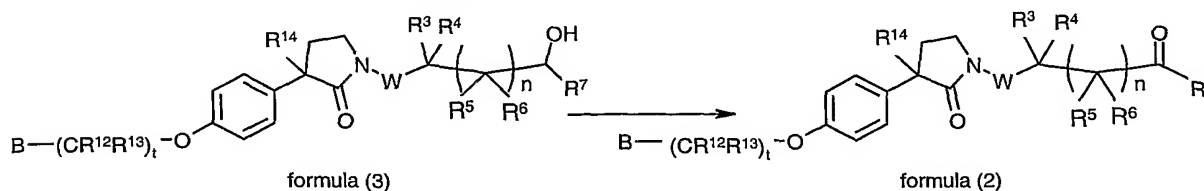


10

Scheme 2b

a suitable reagent is an aqueous acid (eg a mineral acid such as hydrochloric acid) to hydrolyse the ketal to the diol (Protective Groups in Organic Synthesis; Theordora Greene and Peter Wuts, Wiley-InterScience), followed by treatment with sodium periodate or osmium tetroxide to generate the aldehyde. This can be converted directly to the hydantoin as described above, or reacted with Grignard reagents or alkyl lithiums to prepare secondary alcohols, which can be oxidised to the ketones with an oxidising agent.

c) when Y is an alcohol group so that scheme 2 illustrates the reaction:

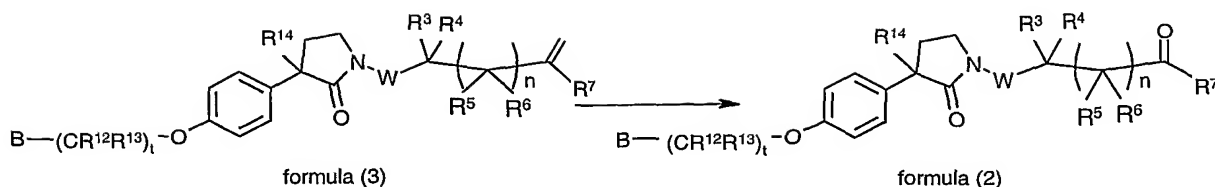


Scheme 2c

20 suitable reagents are oxidising agents.

d) when Y is an alkene group so that scheme 2 illustrates the reaction:

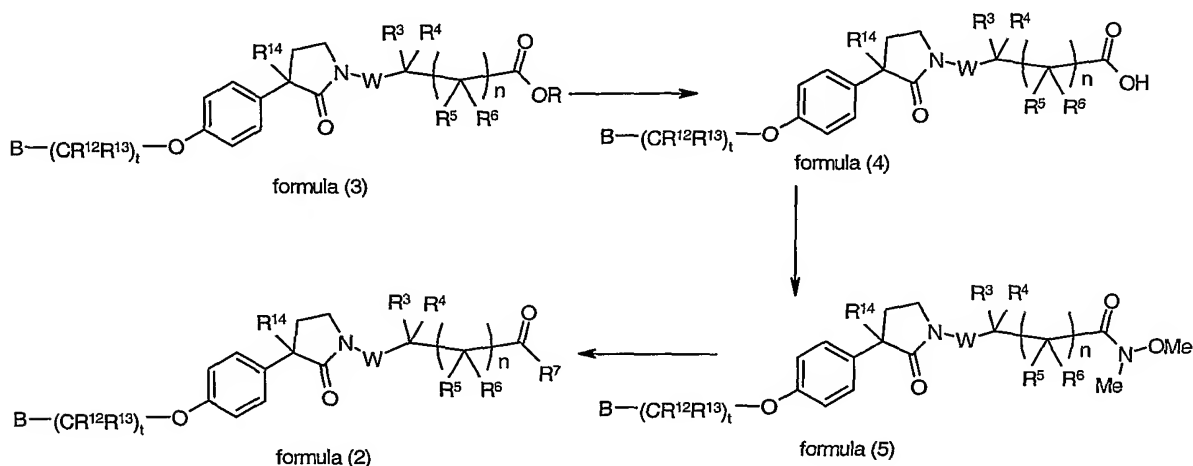
-26-



Scheme 2d

suitable reagents include reagents for ozonolysis, sodium periodate, osmium tetroxide and ruthenium catalysts with a suitable oxidant.

- 5 An alternative to scheme 2a, for the preparation of the aldehyde or ketone of formula (2) from an ester of formula (3) is shown in Scheme 3 which comprises:

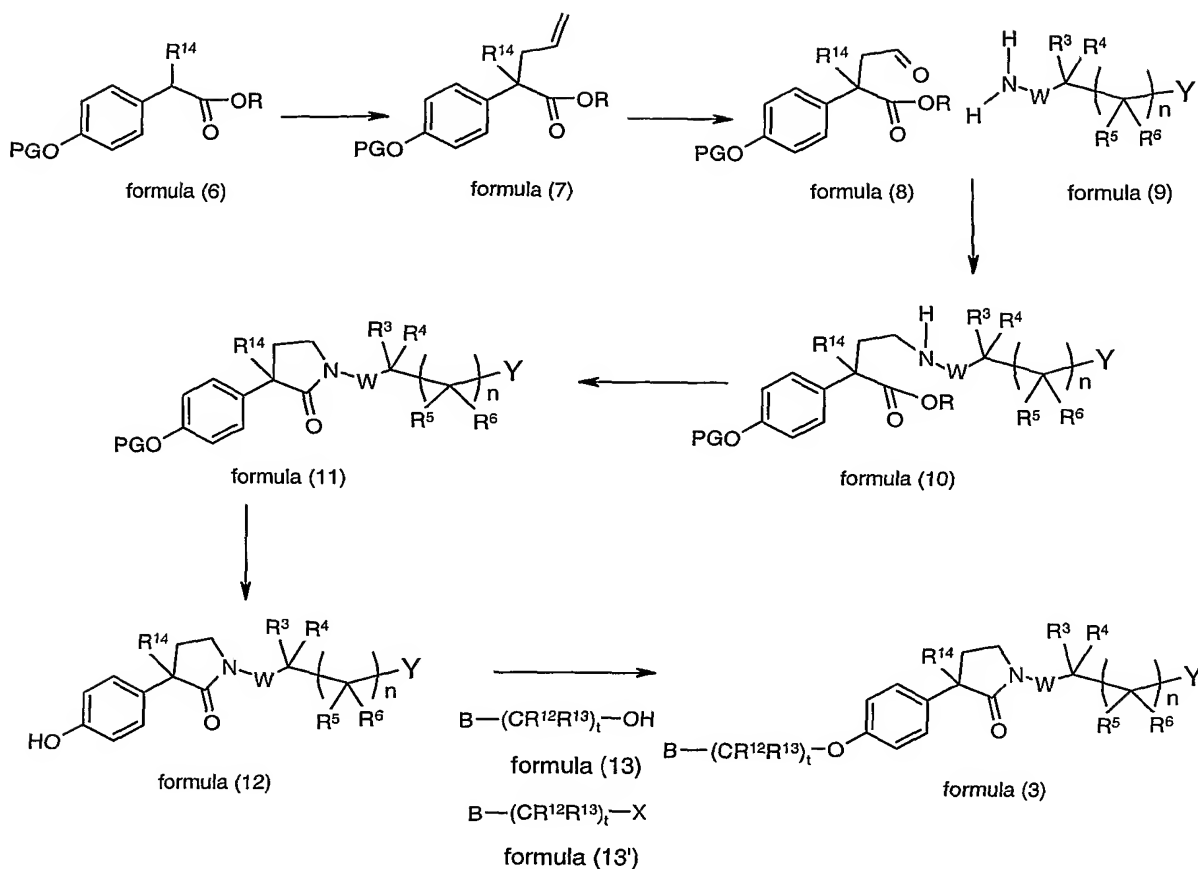


Scheme 3

- a) reacting the ester of formula (3) with a base such as sodium hydroxide, potassium hydroxide or potassium carbonate in alcohols or aqueous alcohols at room temperature to 100°C followed by neutralisation with e.g. acetic acid, to give an acid of formula (4);
- b) reacting the acid of formula (4) with N, O-dimethylhydroxylamine hydrochloride under standard amide coupling conditions or by reacting with triphenylphosphine, carbon tetrabromide and triethylamine in dichloromethane for 10 to 60 minutes (Synth. Commun., 1990, 20, 1105), to give an amide of formula (5); and
- c) reacting the amide of formula (5) with a reducing agent such as diisobutylaluminium hydride or lithium aluminium hydride to give an aldehyde of formula (2) or reacting with Grignard reagents to give a ketone of formula (2).

A compound of formula (3) may be prepared as shown in Scheme 4;

-27-



Scheme 4

The process of Scheme 4 comprises the steps of:

- reacting an ester of formula (6), where PG is a protecting group such as benzyl and R is C₁₋₁₀alkyl, with a base such lithium diisopropylamide or lithium bis(trimethylsilyl)amide in tetrahydrofuran at a temperature of -78°C to 0°C followed by reaction with allyl bromide for 30 minutes to 2 hours to give an allylated product of formula (7);
- reacting the allylated product of formula (7) with ozone, until no more starting compound can be observed by thin layer chromatography or high performance liquid chromatography/mass spectrometry followed by reduction of the resultant ozonide with e.g. dimethylsulphide, triphenylphosphine or polymer supported triphenylphosphine to give an aldehyde of formula (8);
- reacting the aldehyde of formula (8) with an amine or amine salt of formula (9) (where Y is an ester group, a ketal, an alcohol group or an alkene group as defined above) in a solvent such as dichloromethane or dichloroethylene in the presence of a base such as triethylamine or N,N-diisopropylethylamine for 30 minutes to 2 hours before addition of a reducing agent such

as sodium triacetoxyborohydride, sodium borohydride or sodium cyanoborohydride and reacted at room temperature for 2 to 24 hours to give an amine of formula (10);

d) cyclisation of the amine of formula (10) by heating in an inert solvent such as toluene to 90-110°C for 1 to 4 hour to give a lactam of formula (11);

5 e) removal of the protecting group to give a phenol of formula (12) (if a benzyl protecting group is used this can be removed by treatment with palladium on carbon in the presence of either hydrogen or cyclohexene; for a silyl protecting group, mild acid hydrolysis or treatment with fluoride ion can be used);

f) reacting the phenol of formula (12) with an alcohol of formula (13) under Mitsunobu
10 type conditions or by reaction of the phenol with a halide of formula (13') by deprotonation with a base such as sodium hydride, lithium bis(trimethylsilyl)amide in a solvent such as dimethylformamide or tetrahydrofuran at 0°C to 100°C or deprotonation with caesium carbonate in the presence of tetrabutyl ammonium iodide in dimethylsulphoxide at room temperature to 100°C to give a compound of formula (3).

15

A compound of formula (1) can be prepared by removal of protecting groups on the hydantoin directly. The protecting group can be *tert*-butoxycarbonyl (BOC), benzyl (Bn) or benzyloxycarbonyl (cbz). These can be removed by treatment with trifluoroacetic acid or hydrogen chloride in dioxane for the former or by treatment with palladium/hydrogen for the

20 latter two.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the
25 invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the
30 introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts

conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

5 It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley
10 and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl
15 group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl
20 group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a
25 primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting
30 groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis
5 with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using
10 conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses metalloproteinases inhibitory activity, and in particular TACE inhibitory activity. This property may be assessed, for example, using the procedure set out below.

15 Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP13.

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)].
The purified enzyme can be used to monitor inhibitors of activity as follows: purified
20 proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl₂, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH₂ in
25 the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λ_{ex} 328nm and λ_{em} 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the $[\text{Fluorescence}_{\text{plus inhibitor}} - \text{Fluorescence}_{\text{background}}]$ divided by the $[\text{Fluorescence}_{\text{minus inhibitor}} - \text{Fluorescence}_{\text{background}}]$.

A similar protocol can be used for other expressed and purified pro MMPs using
30 substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNF- α convertase enzyme (TACE) may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The

5 purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH₂ in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM CaCl₂), at 26°C for 4 hours. The amount of inhibition is

10 determined as for MMP13 except λ_{ex} 485nm and λ_{em} 538nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-

15 fold excess of Fmoc-amino acid and HBTU. Ser¹ and Pro² were double-coupled. The following side chain protection strategy was employed; Ser¹(But), Gln⁵(Trityl), Arg^{8,12}(Pmc or Pbf), Ser^{9,10,11}(Trityl), Cys¹³(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2 hours at 70°C with 1.5-2 equivalents of

20 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by

25 evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

The compounds of this invention have been found to be active against TACE (causing

30 greater than 50% inhibition) at less than 10 μ M, and in particular 130nM of compound 6 gave 50% inhibition.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274
5 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

10 Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNF- α production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M.
15 Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research
20 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNF- α production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNF- α . 160 μ l of heparinized (10Units/ml) human blood obtained from volunteers, was added to the plate and
25 incubated with 20 μ l of test compound (duplicates), in RPMI1640 + bicarbonate, penicillin, streptomycin, glutamine and 1% DMSO, for 30 min at 37°C in a humidified (5%CO₂/95%air) incubator, prior to addition of 20 μ l LPS (E. coli. 0111:B4; final concentration 10 μ g/ml). Each assay includes controls of neat blood incubated with medium alone or LPS (6 wells/plate of each). The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged
30 (2000rpm for 10 min; 4°C), plasma harvested (50-100 μ l) and stored in 96 well plates at -70°C before subsequent analysis for TNF- α concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) *Biochem J.* 323:483-488.

5

In vivo assessment**Test as an anti-TNF agent**

The ability of the compounds of this invention as *in vivo* TNF- α inhibitors is assessed in the rat. Briefly, groups of female Wistar Alderley Park (AP) rats (90-100g) are dosed with
 10 compound (5 rats) or drug vehicle (5 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.) 1 hour prior to lipopolysaccharide (LPS) challenge (30 μ g/rat i.v.). Sixty minutes following LPS challenge rats are anaesthetised and a terminal blood sample taken via the posterior vena cavae. Blood is allowed to clot at room temperature for 2 hours and serum samples obtained. These are stored at -20°C for TNF- α ELISA and
 15 compound concentration analysis.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF-}\alpha = \frac{\text{Mean TNF-}\alpha \text{ (Vehicle control)} - \text{Mean TNF-}\alpha \text{ (Treated)} \times 100}{\text{Mean TNF-}\alpha \text{ (Vehicle control)}}$$

Test as an anti-arthritis agent

20 Activity of a compound as an anti-arthritis is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) *J. Exp. Med.* 146:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freund's incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

25 Pharmaceutical Compositions

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

30

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical

administration as an ointment or cream or for rectal administration as a suppository. The composition may also be in a form suitable for inhalation.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

5 The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease
10 condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore a further aspect of the present invention provides a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined
15 hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy. Also provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF α . Further provided is a compound of formula (1), or a
20 pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as
25 defined hereinbefore, is provided for use in a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal such as man. A compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, is also provided for use in a method of treating a respiratory disorder such as asthma or COPD in a warm-blooded animal such as man.

30 According to an additional aspect of the invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament. Also provided is a compound of formula (1),

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF- α . Further provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use as a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal such as man. A compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use as a medicament in the treatment of a respiratory disorder such as asthma or COPD in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF- α in a warm-blooded animal such as man. Also provided is the use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular the use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal such as man. The use of a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, is also provided in the manufacture of a medicament for use in the treatment of a respiratory disorder such as asthma or COPD in a warm-blooded animal such as man.

According to another aspect of the invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF- α in a warm-blooded animal such as man. Also provided is a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal such as man. A compound of formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, is also provided for use in the treatment of a respiratory disorder such as asthma or COPD in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of producing a metalloproteinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to a further feature of this aspect of the invention there is provided a method of producing a TACE inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1). According to this further feature of this aspect of the invention there is provided a method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1). Also provided is a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1). Further provided is a method of treating a respiratory disorder such as asthma

or COPD in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the
5 development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the
10 invention described herein also apply.

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of various immunological, inflammatory or malignant disease states which would benefit from the inhibition of TACE.

If formulated as a fixed dose such combination products employ the compounds of this
15 invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Examples

20 The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent
25 was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size,
30 the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut ST".

Where an "IsoluteTM SCX column" is referred to, this means a column containing

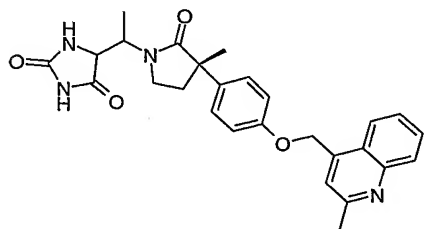
benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industrial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where Flashmaster II is referred to, this means a UV driven automated chromatography unit supplied by Jones;

- 5 (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- 10 (vi) when given, ^1H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using CDCl_3 as the solvent unless otherwise stated; coupling constants (J) are given in Hz;
- (vii) chemical symbols have their usual meanings; SI units and symbols are used;
- 15 (viii) solvent ratios are given in percentage by volume;
- (ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the
- 20 positive mass ion - $(\text{M}+\text{H})^+$;
- (x) LCMS (liquid chromatography mass spectrometry) characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05%
- 25 formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(\text{M}+\text{H})^+$ and
- (xi) the following abbreviations are used:
- 30 min minute(s);
- h hour(s);
- d day(s);

	DMSO	dimethyl sulphoxide;
	DMF	<i>N</i> -dimethylformamide;
	DCM	dichloromethane;
	NMP	<i>N</i> -methylpyrrolidinone;
5	DIAD	di- <i>isopropyl</i> azodicarboxylate;
	LHMDS or LiHMDS	lithium bis(trimethylsilyl)amide;
	MeOH	methanol;
	RT	room temperature;
	TFA	trifluoroacetic acid;
10	EtOH	ethanol;
	EtOAc	ethyl acetate;
	THF	tetrahydrofuran;
	DIBAL	di- <i>isobutyl</i> aluminium hydride;
	NMO	4-methylmorpholine <i>N</i> -oxide; and
15	TPAP	tetra- <i>n</i> -propylammonium perruthenate (VII)

EXAMPLE 1

(R/S)-5-(1-{3-Methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}ethyl)imidazolidine-2,4-dione



20

To a stirred solution of 2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionaldehyde (540mg, 1.34mmol) in EtOH (5ml) and water (5ml) was added ammonium carbonate (770mg, 8.0mmol) and potassium cyanide (174mg, 2.68mmol). The mixture was heated to reflux for 1.5 h before addition of a further portion of ammonium carbonate (300mg, 3.1mmol). Heating was continued for 1 h and the solution left to stand at
 25 carbonate (300mg, 3.1mmol). Heating was continued for 1 h and the solution left to stand at RT for 40 h. The solution was reheated to reflux for 3 h, then evaporated under reduced pressure to give a yellow solid. The residue was partitioned between DCM (30ml) and water (30ml). The aqueous phase was extracted with DCM (20ml) and the combined organic phases

were dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 2% MeOH / DCM) to give the product, as a mixture of 4 diastereoisomers, as a white foam (200mg, 0.42mmol); MS: 473.

5 The starting material 2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxo-
pyrrolidin-1-yl}propionaldehyde was prepared as follows :

i) To a solution of methyl (R)-2-[3-(4-hydroxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]propionate§ (725mg, 2.62mmol) in DMSO (30ml) was added 4-chloromethyl-2-methylquinoline† (500mg, 2.62mmol), caesium carbonate (1.7g, 5.2 mmol) and tetra-*n*-butylammonium iodide (1.0g, 2.6 mmol). The resultant solution was stirred at 60 °C for 75 min. The reaction mixture was allowed to cool then diluted with EtOAc (200ml) and washed with brine (3x100ml). The organic phase was dried (Na₂SO₄), evaporated and purified by chromatography (Flashmaster II, 50g silica bond elute, eluent 50→100% EtOAc / isohexane) to give methyl (R)-2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionate (780mg, 1.8mmol) as an oil; NMR 1.43 (d, 3H), 1.55 (s, 3H), 2.21 (m, 1H), 2.41 (m, 1H), 2.75 (s, 3H), 3.31 (m, 1H), 3.45 (m, 1H), 3.74 (s, 3H), 4.93 (q, 1H), 5.48 (s, 2H), 6.99 (d, 2H), 7.36 (d, 2H), 7.45 (s, 1H), 7.52 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS 433.

ii) Methyl (R)-2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionate (780mg, 1.8mmol) was azeotroped with toluene, dissolved in DCM (10ml) and the solution cooled to -78°C . To this was added a solution of DIBAL (1.0M in DCM, 3.6mmol, 3.6ml) dropwise over 10 min. The solution was stirred at -78°C for 2 h, before quenching with saturated ammonium chloride solution and allowing to warm to RT. The solution was then diluted with water (20ml) and DCM (20ml) and the aqueous phase extracted with DCM (3x30ml). The combined organic layers were dried (Na_2SO_4), concentrated and purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 50 \rightarrow 100% EtOAc / isohexane) to give 2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionaldehyde as a 2:1 mixture of diastereoisomers (540mg, 1.34mmol); NMR 1.37 (d, 3H, major isomer), 1.40 (d, 3H, minor isomer), 1.56 (s, 3H, minor isomer), 1.59 (s, 3H, major isomer), 2.22-2.28 (m, 1H), 2.45-2.51 (m, 1H), 2.75 (s, 3H), 3.26-3.36 (m, 2H), 4.71 (q, 1H), 5.49 (s, 2H), 7.00 (d, 2H, minor

isomer), 7.01 (d, 2H, major isomer), 7.36 (d, 2H, major isomer), 7.40 (d, 2H, minor isomer), 7.45 (s, 1H), 7.53 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS: 403.

§ The synthesis of methyl (R)-2-[3-(4-hydroxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]propionate has been described in WO99/18974 and has CAS Registry number 223406-12-0.

† The synthesis of the 4-chloromethyl-2-methylquinoline has been described in WO99/65867 and has CAS Registry number 288399-19-9.

Alternatively (R/S)-5-(1-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}ethyl)imidazolidine-2,4-dione may be prepared as follows:
To a stirred solution of 2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionaldehyde (100mg, 0.25mmol) in EtOH (3ml) and water (3ml) was added ammonium carbonate (150mg, 1.5mmol) and potassium cyanide (33mg, 0.5mmol). The mixture was heated to reflux for 4 h. The solution was left to stand at RT overnight then heated at reflux for 5 h and again stood at RT for 3 d. The solution was evaporated under reduced pressure to give a yellow solid. The residue was partitioned between EtOAc (30ml) and brine (30ml). The aqueous phase was extracted with EtOAc (30ml) and the combined organic phases dried (Na₂SO₄) and evaporated. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 3% MeOH / DCM) to give the product, as a mixture of 2 diastereoisomers, as a white foam (19mg, 0.04mmol); MS: 473.

The starting material 2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionaldehyde was prepared as follows :

i) Methyl 2-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}propionate (330mg, 0.76mmol) [*J. Med. Chem.*, 2002, **45**, 4954.] was dissolved in THF (6ml). To this was added a solution of lithium borohydride (2.0M in THF, 1.68mmol, 0.85ml). The solution was stirred at RT for 1 h, before quenching with saturated ammonium chloride solution. The solution was then diluted with DCM (20ml) and the aqueous phase extracted with DCM (10ml). The combined organic layers were dried (Na₂SO₄), concentrated and purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 50→100% EtOAc / isohexane) to give 1-(2-hydroxy-1-methylethyl)-3-methyl-3-[4-(2-methylquinolin-4-

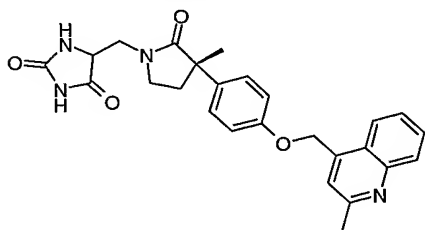
-42-

ylmethoxy)phenyl]pyrrolidin-2-one as a single diastereoisomer (100mg, 0.25mmol); NMR (CDCl₃) 1.19 (d, 3H), 1.53 (s, 3H), 2.17 (m, 1H), 2.42 (m, 1H), 2.69 (m, 1H) 2.75 (s, 3H), 3.28 (m, 1H), 3.40 (m, 1H) 3.64 (m, 1H) 3.75 (m, 1H), 4.15 (m, 1H), 5.48 (s, 2H), 7.00 (d, 2H), 7.35 (d, 2H), 7.43 (s, 1H), 7.53 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS: 5 405.

ii) 1-(2-Hydroxy-1-methylethyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (100mg, 0.25mmol) was dissolved in DCM (2.5ml). To this was added a solution of Dess-Martin reagent (15% w/v in DCM, 0.7ml). The solution was stirred at RT for 3 h and the reaction mixture then diluted with EtOAc (40ml), washed 10 with brine (20ml), dried (Na₂SO₄) and evaporated. The resultant product was used in the final step without purification; MS: 403.

EXAMPLE 2

(R/S)-5-{3-Methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione 15



To a stirred solution of {3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetaldehyde (450mg, 1.16mmol) in EtOH (5ml) and water (5ml) was added ammonium carbonate (668mg, 7.0mmol) and potassium cyanide (151mg, 2.3mmol). 20 The mixture was heated to reflux for 3 h before addition of a further portion of ammonium carbonate (300mg, 3.1mmol). Heating was continued for 1 h and the solution allowed to cool and evaporated. The residue was partitioned between DCM (30ml) and water (30ml). The aqueous phase was extracted with DCM (30ml) and the combined organic phases dried (Na₂SO₄) and evaporated. The crude product was purified by chromatography (Flashmaster 25 II, 20g silica bond elute, eluent 2%→5% MeOH in DCM) to give the product, as a mixture of 2 diastereoisomers, as a white foam (130mg, 0.28mmol); MS: 457.

The starting material {3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetaldehyde was prepared as follows :

- i) To a solution of methyl 2-(4-benzyloxyphenyl)-2-methyl-4-oxobutanoate‡ (3.71g, 11.9mmol) in 1,2-dichloroethane was added methyl glycinate hydrochloride (1.6g, 12.7mmol) and diisopropylethylamine (2.3ml, 13.2mmol). The resultant solution was stirred at RT for 90 min before addition of sodium triacetoxyborohydride (3.3g, 15.5mmol). The reaction mixture was stirred for a further 2 h, before addition of DCM (150ml) and brine (150ml). The aqueous phase was extracted with DCM (150ml). The combined organic phases were dried (Na₂SO₄) and evaporated. The resultant oil was dissolved in toluene (50ml) and heated to 90°C for 1 h, allowed to cool, evaporated and purified by chromatography (Flashmaster II, 100g silica bond elute, eluent 20% EtOAc / isohexane) to give methyl [3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetate (2.18g, 6.2 mmol) as a white solid; NMR 1.55 (s, 3H), 2.19 (m, 1H), 2.43 (m, 1H), 3.41 (m, 2H), 3.73 (s, 3H), 4.13 (s, 2H), 5.04 (s, 2H), 6.93 (d, 2H) 7.29-7.43 (m, 7H); MS 354.
- ii) To a solution of methyl [3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetate (2.18g, 6.2 mmol) in EtOH (50ml) was added cyclohexene (6.3 ml, 62mmol) and 10% Pd/C (1.0g). The reaction mixture was heated under reflux for 1 h. The reaction mixture was allowed to cool and evaporated to give methyl [3-(4-hydroxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetate as an oil (1.6g, 60.8mmol); NMR 1.55 (s, 3H), 2.19 (m, 1H), 2.42 (m, 1H), 3.44 (m, 2H), 3.74 (s, 3H), 4.13 (s, 2H), 6.74 (d, 2H), 7.24 (d, 2H). MS 264.
- iii) To a solution of methyl [3-(4-hydroxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetate (1.0g, 3.8mmol) in DMSO (30ml) was added 4-chloromethyl-2-methylquinoline† (725mg, 3.8mmol), caesium carbonate (2.48g, 7.6 mmol) and tetra-*n*-butylammonium iodide (1.4g, 3.8 mmol). The resultant solution was stirred at 60 °C for 90 min. The reaction mixture was allowed to cool then diluted with EtOAc (200ml) and washed with brine (3x100ml). The organic phase was dried (Na₂SO₄), evaporated and purified by chromatography (Flashmaster II, 50g silica bond elute, eluent 50→100% EtOAc / isohexane) to give methyl {3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetate (1.0g, 2.4mmol) as an oil; NMR 1.57 (s, 3H), 2.21 (m, 1H), 2.44 (m, 1H), 2.75 (s, 3H), 3.44 (m, 2H), 3.74 (s, 3H), 4.15 (s, 2H), 5.49 (s, 2H), 7.00 (d, 2H), 7.39 (d, 2H), 7.47 (s, 1H), 7.53 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS 419.

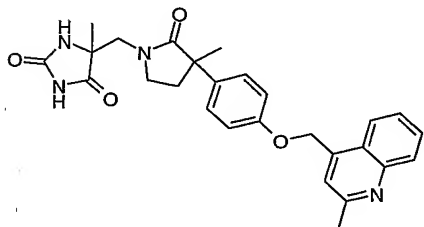
iv) Methyl {3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetate (500mg, 1.16mmol) was azeotroped with toluene and dissolved in DCM (6ml) and the solution cooled to -78°C . To this was added a solution of DIBAL (1.0M in DCM, 2.3mmol, 2.3ml) dropwise over 10 min. The solution was stirred at -78°C for 1 h, before
5 quenching with saturated ammonium chloride solution and allowing to warm to RT. The solution was then diluted with water (10ml) and DCM (10ml) and the aqueous phase extracted with DCM (3x30ml). The organic phase was dried (Na_2SO_4), and evaporated to give the crude aldehyde which was used without further purification; MS: 489.

10 ‡ The synthesis of methyl 2-(4-benzyloxyphenyl)-2-methyl-4-oxobutanoate has been described in *J. Med. Chem.*, 2002, **45**, 4954., WO99/18974 and has CAS Registry number 223406-00-6.

† The synthesis of the 4-chloromethyl-2-methylquinoline has been described in WO99/65867
15 and has CAS Registry number 288399-19-9.

EXAMPLE 3

5-Methyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione



20

To a stirred solution of 3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-1-(2-oxopropyl)pyrrolidin-2-one (163mg, 0.41mmol) in EtOH (2ml) and water (2ml) was added ammonium carbonate (250mg, 2.6mmol) and potassium cyanide (55mg, 0.85mmol). The mixture was heated to 60°C for 2.5 h and then 16 h at RT. Silica gel (2g) was added and the
25 suspension evaporated. The resultant powder was applied to the top of a 10g bond elute and purified on a Flashmaster II eluting with 0%→10% EtOH in DCM to give the product, as a mixture of 2 diastereoisomers, as a white foam (99mg, 0.21mmol); NMR 1.23 (s, 1.5H), 1.24 (s, 1.5H), 1.376 (s, 1.5H), 1.378 (s, 1.5H), 2.07 (m, 1H), 2.25 (m, 1H), 2.67 (s, 3H), 3.47 (ABq,

1H), 3.68 (d, 0.5H), 5.58 (s, 1H), 5.59 (s, 1H), 7.06 (d, 1H), 7.09 (d, 1H), 7.29 (d, 1H), 7.31 (d, 1H), 7.56 (s, 1H), 7.59 (m, 1H), 7.75 (m, 1H), 7.96 (s, 1H), 8.00 (d, 1H), 8.10 (d, 1H), 10.67 (s, 0.5H), 10.68 (s, 0.5H); MS: 473.

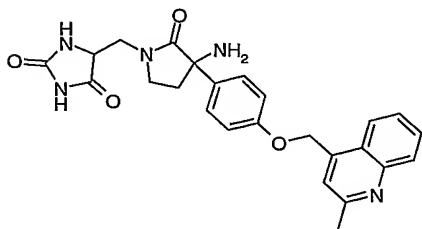
- 5 The starting material 3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-1-(2-oxopropyl)pyrrolidin-2-one was prepared as follows :
- i) To a solution of methyl 2-(4-benzyloxyphenyl)-2-methyl-4-oxobutanoate (521mg, 1.67mmol) in 1,2-dichloroethane (10ml) was added 2-amino-1-propanol (0.18ml, 2.33mmol). The resultant solution was stirred at RT for 1 h before addition of sodium
- 10 triacetoxyborohydride (496mg, 2.34mmol). The reaction mixture was stirred for a further 1h and stood at RT for 72 h before addition of DCM (20ml) and brine (20ml). The organic phase was dried (Na₂SO₄) and evaporated. The resultant oil was dissolved in toluene (20ml) and heated to 90°C for 2 h, allowed to cool and evaporated. The resultant oil was dissolved in EtOH (10ml) and placed under an argon atmosphere. Cyclohexene (1.2ml, 17mmol) and 10%
- 15 palladium on charcoal (200mg) were added and the resultant mixture heated to reflux for 2 h. The reaction mixture was allowed to cool, filtered and evaporated to an oil (440mg). The crude product was dissolved in DMSO (4ml). To this caesium carbonate (1.1g, 3.38mmol), tetra-n-butylammonium iodide (620mg, 1.68mmol) and 4-chloromethyl-2-methylquinoline (333mg, 1.74mmol) were added and the mixture heated to 60°C for 45 min. The reaction
- 20 mixture was partitioned between EtOAc (20ml) and brine (20ml). The organic phase was washed with brine (2x20ml), dried and evaporated. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 100% EtOAc) to give 1-(2-hydroxypropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one as an oil (475mg); MS: 405.
- 25 ii) To a solution of 1-(2-hydroxypropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one in anhydrous DCM (7ml) was added NMO (240mg, 1.8mmol) and 4A molecular sieves (660mg). The reaction mixture was stirred for 10 min before addition of TPAP (22mg, 0.06mmol), stirring was continued for 20 min and the reaction mixture was poured onto a 5g Silica bond elute and washed with DCM/MeOH (1:1).
- 30 The solvent was evaporated to give the crude product which was purified by chromatography (Flashmaster II, eluent 100% EtOAc) to give 3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-1-(2-oxopropyl)pyrrolidin-2-one as an oil (130mg, 0.32mmol); NMR

-46-

(400MHz, DMSO), 1.43 (s, 3H), 2.10 (s, 3H), 2.13 (m, 1H), 2.31 (m, 1H), 2.67 (s, 3H), 4.17 (ABq, 2H), 5.58 (s, 2H), 7.09 (d, 2H), 7.37 (d, 2H), 7.56 (s, 1H), 7.59 (m, 1H), 7.74 (m, 1H), 7.97 (d, 1H), 8.11 (d, 1H).

5 **EXAMPLE 4**

5-{3-Amino-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione dihydrochloride



To a stirred solution of acetyl chloride (0.5ml) in MeOH (5ml) was added *tert*-butyl {1-(2,5-dioxoimidazolidin-4-ylmethyl)-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-3-yl}carbamate (183mg, 0.33mmol). The reaction was stirred at RT for 90 min during which time a white precipitate formed. The reaction mixture was filtered to give a white crystalline solid (90mg, 0.17mmol) as a mixture of diastereoisomers; MS: 460. The mother liquors were evaporated to give a further 60mg of product as an off white solid.

5-{3-Amino-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione dihydrochloride (50mg) was separated by chiral chromatography (instrument: Gilson, column: Merck 50mm 20µm Chiralcel OJ, eluent EtOH/MeOH/TEA 50/50/0.5 at 35ml/min) to give 4 isomers as the free base, isomer A (8mg, 79% purity), MS:460; isomer B (11mg, 64% purity), MS: 460; isomer C (10mg, 63% purity) MS: 460 and isomer D (10mg, 75% purity) MS: 460.

The starting material *tert*-butyl {1-(2,5-dioxoimidazolidin-4-ylmethyl)-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxo-pyrrolidin-3-yl}carbamate was prepared as follows :

i) To a solution of methyl 2-(4-benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-4-oxobutanoate (CAS Registry number 223407-41-8) (1.15g, 2.8mmol) in 1,2-dichloroethane (15ml) was added methyl glycinate hydrochloride (390mg, 3.1mmol) and diisopropylethylamine (0.54ml, 0.31 mmol). The resultant solution was stirred at RT for 60

min before addition of sodium triacetoxyborohydride (770mg, 3.6mmol). The reaction mixture was stirred for a further 2 h, before addition of DCM (35ml) and brine (50ml). The aqueous phase was extracted with DCM (50ml). The combined organic phases were dried (Na₂SO₄) and evaporated. The resultant oil was dissolved in toluene (30ml) and heated to

5 90°C for 90 min, allowed to cool, evaporated and purified by chromatography (Flashmaster II, 50g silica bond elute, eluent 20% to 80% EtOAc / isohexane) to give methyl 3-(4-benzyloxyphenyl)-3-*tert*-butoxycarbonylamino-2-oxopyrrolidin-1-ylacetate (2.18g, 6.2 mmol) as a colourless oil; NMR (400MHz, CDCl₃) 1.40 (br. s, 9H), 2.87 (br. s, 2H), 3.38-3.51 (m, 2H), 3.68 (s, 3H), 3.90 (d, 1H), 4.36 (br.d, 1H), 5.05 (s, 2H), 5.50 (br. s, 1H), 6.95 (d, 2H),
10 7.31-7.45 (m, 7H).

ii) To a solution of methyl 3-(4-benzyloxyphenyl)-3-*tert*-butoxycarbonylamino-2-oxopyrrolidin-1-ylacetate (800mg, 1.8mmol) in EtOH (25ml) was added cyclohexene (1.8 ml, 18mmol) and 10% Pd/C (400mg). The reaction mixture was heated under reflux for 80 min. The reaction mixture was allowed to cool and evaporated to give methyl [3-*tert*-

15 butoxycarbonylamino-3-(4-hydroxyphenyl)-2-oxopyrrolidin-1-yl]-acetate as white foam (660mg, 1.8mmol); NMR (400MHz CDCl₃) 1.40 (s, 9H), 2.86 (br. s, 2H), 3.42-3.53 (m, 2H), 3.48 (s, 3H), 3.90 (m, 1H), 4.34 (br. d, 1H), 5.56 (br. s, 1H), 6.42 (br. s, 1H), 6.67 (d, 2H), 7.29 (d, 2H).

iii) To a solution of methyl [3-*tert*-butoxycarbonylamino-3-(4-hydroxyphenyl)-2-oxopyrrolidin-1-yl]acetate (600mg, 1.6mmol) in DMSO (15ml) was added 4-chloromethyl-2-methylquinoline (320mg, 1.7mmol), caesium carbonate (1.08g, 3.3mmol) and tetra-*n*-butylammonium iodide (610mg, 1.65mmol). The resultant solution was stirred at 60 °C for 70 min. The reaction mixture was allowed to cool then diluted with EtOAc (90ml) and washed with brine (3x45ml). The organic phase was dried (Na₂SO₄), evaporated and purified by
25 chromatography (Flashmaster II, 50g silica bond elute, eluent 40→80% EtOAc / isohexane) to give methyl {3-*tert*-butoxycarbonylamino-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetate (525mg, 1.0mmol) as an oil; NMR (400MHz, CDCl₃) 1.41 (br. s, 9H), 2.75 (s, 3H), 2.89 (br. s, 2H), 3.43 (m, 1H), 3.52 (m, 1H), 3.70 (m, 1H), 3.90 (1H,d), 4.40 (br. d, 1H), 5.49 (s, 2H), 5.54 (s, 1H), 7.02 (d, 2H), 7.44 (s, 1H), 7.49 (d, 2H), 7.53 (m, 1H),
30 7.71 (m, 1H), 7.91 (d, 1H), 8.08 (d, 1H).

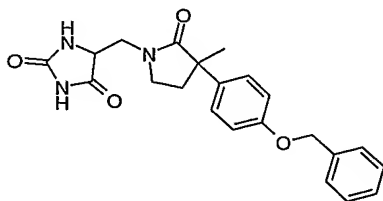
iv) Methyl {3-*tert*-butoxycarbonylamino-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetate (525mg, 1.01mmol) was dissolved in anhydrous DCM (10ml) and

the solution cooled to -78°C . To this was added a solution of DIBAL (1.0M in DCM, 2.0mmol, 2.0ml) dropwise over 2 min. The solution was stirred at -78°C for 2.5 h, before adding a further portion of DIBAL (1.0M in DCM, 1.0mmol, 1.0ml). The reaction mixture was stirred for a further 30 min before quenching with saturated ammonium chloride solution (15ml) and allowing to warm to RT. The solution was then diluted with water (20ml) and DCM (20ml). This was then filtered and the organic phase dried (Na_2SO_4) and evaporated to give the crude aldehyde (370mg) which was used without further purification; MS: 490.

v) To a stirred solution of tert-butyl [3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxo-1-(2-oxoethyl)pyrrolidin-3-yl]carbamate (365mg, 0.75mmol) in EtOH (5ml) and water (5ml) was added ammonium carbonate (430mg, 4.5mmol) and potassium cyanide (98mg, 1.5mmol). The mixture was heated to 65°C for 2 h before addition of a second portion of ammonium carbonate (430mg, 4.5mmol). The reaction was heated for further 1 h. The reaction mixture was allowed to cool and then evaporated. The residue was partitioned between DCM (20ml) and water (30ml). The aqueous phase extracted with DCM (20ml) and the combined organic phases dried (Na_2SO_4) and evaporated to a white foam. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 2% to 20% MeOH / DCM) to give the product, as a mixture of 2 diastereoisomers (186mg, 0.33mmol).

EXAMPLE 5

20 **5-[3-(4-Benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-ylmethyl]imidazolidine-2,4-dione**



To a stirred solution of [3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetaldehyde (343mg, 1.06mmol) in EtOH (5ml) and water (5ml) was added ammonium carbonate (610mg, 6.35mmol) and potassium cyanide (140mg, 2.15mmol). The mixture was heated to reflux for 3 h. The solution was allowed to cool and evaporated. The residue was partitioned between EtOAc (20ml) and water (20ml). The organic phase was washed with brine (20ml), dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 0% \rightarrow 10% MeOH in DCM) to give the product, as a 1:1 mixture of diastereoisomers, as a white foam (64mg, 0.16mmol); NMR 1.38 (s, 3H), 2.07 (m,

-49-

1H), 2.26 (m, 1H), 3.17-3.66 (m, 4H), 4.25 (s, 1H), 5.08 (s, 2H), 6.92-6.96 (m, 2H), 7.27-7.45 (m, 7H), 8.02 (s, 0.5H), 8.05 (s, 0.5H), 10.70 (s, 1H); MS: 394.

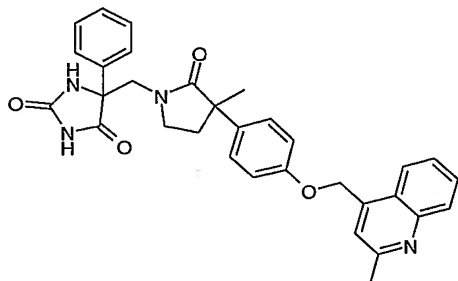
The starting material [3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetaldehyde

5 was prepared as follows :

- i) Methyl [3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetate (440mg, 1.25mmol) (example 2 step i)) was dissolved in DCM and cooled to -78°C. A solution of DIBAL (1.0M in DCM, 2.5ml, 2.5mmol) was added and the reaction mixture stirred at -78°C for 1 h. The reaction was quenched by pouring onto sodium sulphate decahydrate. The resultant suspension was filtered and evaporated to give [3-(4-benzyloxyphenyl)-3-methyl-2-oxopyrrolidin-1-yl]acetaldehyde as an oil which was used in the next stage without further purification; MS: 324.

EXAMPLE 6

- 15 **5-{3-Methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}-5-phenylimidazolidine-2,4-dione**



- To a stirred solution of 3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-1-(2-oxo-2-phenylethyl)pyrrolidin-2-one (90mg, 0.19mmol) in EtOH (2ml) and water (2ml) was added ammonium carbonate (110mg, 1.15mmol) and potassium cyanide (25mg, 0.38mmol). The mixture was heated to 56°C for 10 d. Silica gel (1g) was added and the suspension evaporated. The resultant powder was applied to the top of a 5g bond elute and chromatographed (Flashmaster II, eluent EtOAc) to give product of low purity (24mg). This was further purified by preparative TLC to give the title compound (5mg, 0.009mmol) as a 1:1 mixture of diastereoisomers. MS: 535.

The starting material 3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-1-(2-oxo-2-phenylethyl)pyrrolidin-2-one was prepared as follows:

- i) To a solution of methyl 2-(4-benzyloxyphenyl)-2-methyl-4-oxobutanoate (4.90g, 15.7mmol) in 1,2-dichloroethane (100ml) was added 2,2-dimethyl-1,3-dioxolan-4-ylmethylamine (3.3ml, 25.4mmol). The resultant solution was stirred at RT for 60 min before addition of sodium triacetoxyborohydride (5.3g, 25mmol). The reaction mixture was stirred for a further 1 h and stood at RT overnight before addition of DCM (100ml) and brine (100ml). The organic phase was washed with saturated sodium bicarbonate solution (100ml), dried (Na_2SO_4) and evaporated. The resultant oil (6.53g) was dissolved in EtOH (100ml) and placed under an argon atmosphere. Cyclohexene (16ml, 160mmol) and 10% palladium on charcoal (2.0g) were added and the resultant mixture heated to reflux for 2.5 h. The reaction mixture was allowed to cool, filtered and evaporated to an oil (5.54g). The crude product was dissolved in DMSO (60ml). To this caesium carbonate (10.25g, 31.5mmol), tetra-n-butylammonium iodide (5.8g, 15.7mmol) and 4-chloromethyl-2-methylquinoline (3.0g, 15.7mmol) were added and the mixture heated to 60°C for 40 min. The reaction mixture was partitioned between EtOAc (200ml) and brine (100ml). The organic phase was washed with brine (2x100ml), dried and evaporated. The crude product was purified by chromatography (Flashmaster II, eluent 100% EtOAc) to give 1-(2,2-dimethyl-[1,3]-dioxolan-4-ylmethyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one as an oil (3.74g, 8.1mmol) as a 1:1 mixture of diastereoisomers; NMR 1.25 (s, 3H), 1.30 (s, 1.5H), 1.35 (s, 1.5H), 1.388 (s, 1.5H), 1.393 (s, 1.5H), 2.09 (m, 1H), 2.30 (m, 1H), 2.67 (s, 3H), 3.27-3.48 (m, 4H), 3.58 (m, 1H), 3.97 (m, 1H), 4.22 (m, 1H), 5.59 (s, 2H), 7.08 (d, 1H), 7.09 (d, 1H), 7.31-7.35 (m, 2H), 7.55 (m, 1H), 7.58 (m, 1H), 7.75 (m, 1H), 7.97 (d, 1H), 8.11 (d, 1H); MS: 461.
- ii) 1-(2,2-Dimethyl-[1,3]-dioxolan-4-ylmethyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one was dissolved in hydrochloric acid (2M, 40ml) and left to stand for 20 min, during which time a thick white precipitate formed. The suspension was basified with saturated sodium bicarbonate solution and extracted with DCM (2x150ml). The organic phase was dried (Na_2SO_4) and evaporated to give 1-(2,3-dihydroxypropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (3.3g, 7.8mmol); NMR 1.39 (s, 3H), 2.08 (m, 1H), 2.30 (m, 1H), 2.67 (s, 3H), 3.10-3.44 (m, 6H), 3.66 (m, 1H), 4.52-4.57 (m,

1H), 4.76-4.78 (m, 1H), 5.58 (s, 2H), 7.078 (d, 1H), 7.084 (d, 1H), 7.33 (d, 1H), 7.34 (d, 1H), 7.56 (s, 1H), 7.59 (m, 1H), 7.75 (m, 1H), 7.97 (d, 1H), 8.10 (d, 1H); MS: 421.

iii) 1-(2,3-Dihydroxypropyl)-3-methyl-3-[4-(2-methylquinolin-4-

ylmethoxy)phenyl]pyrrolidin-2-one (1.65g, 3.93mmol) was dissolved in MeOH (50ml) and

5 water (10ml). Sodium periodate was added to the solution and the mixture left to stand for 30 min, during which time a thick white precipitate formed. MeOH was evaporated and the residue partitioned between saturated sodium bicarbonate (50ml) and DCM (50ml). The aqueous phase was extracted with DCM (2x50ml). The combined organic phases were dried (Na₂SO₄) and evaporated. The resultant oil was redissolved in toluene (100ml) and

10 evaporated. This was repeated a further 5 times to give {3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-yl}acetaldehyde as an oil (1.52g, 3.92mmol). MS: 389.

iv) 3-Methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-

yl}acetaldehyde (210mg, 0.54mmol) was dissolved in THF (5ml) in cooled to 0°C. To this solution was added a solution of phenyl magnesium bromide (1.0M in THF, 0.65ml) and

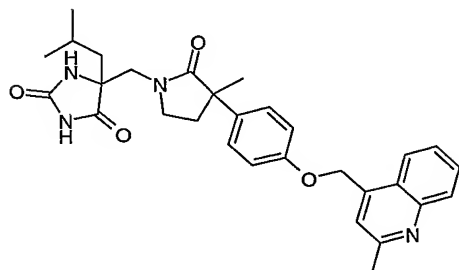
15 solution stirred at 0°C for 1 h. A further portion of phenyl magnesium bromide (1.0M in THF, 0.33ml) was added and the ice-bath removed. The solution was stirred at RT for 20 min before quenching with saturated ammonium chloride (10ml) and portioning between EtOAc (50ml) and brine (50ml). The organic phase was dried (Na₂SO₄) and evaporated. The crude product was purified by chromatography (Flashmaster II, 10g silica bond elute, eluent

20 70%→100% EtOAc in isohexane) to give 1-(2-hydroxy-2-phenylethyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one as a yellow oil (120mg, 0.26mmol); MS: 467.

v) 1-(2-Hydroxy-2-phenylethyl)-3-methyl-3-[4-(2-methylquinolin-4-

ylmethoxy)phenyl]pyrrolidin-2-one (120mg, 0.26mmol) was dissolved in DCM (4ml). NMO

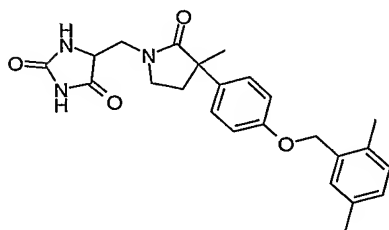
25 (53mg, 0.39mmol) and 4A molecular sieves (300mg) were added. The reaction was stirred for 10 min before addition of TPAP (6mg). The reaction was stirred for 30 min and poured onto a 5g silica bond elute and eluted with EtOAc to give 3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-1-(2-oxo-2-phenylethyl)pyrrolidin-2-one as an oil (90mg, 0.19mmol); MS:465.

EXAMPLE 7**5-Isobutyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione**

5

An analogous method to that described in Example 6 was used except that isobutyl magnesium chloride (2.0M in THF) was used instead of phenyl magnesium bromide (1.0M in THF) to give 5-isobutyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione (6mg, 0.011mmol); MS:515.

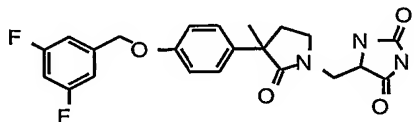
10

EXAMPLE 8**5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione**

15 An analogous method to that described in Example 6 was used to give 5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione 68mg (0.161mmol); NMR (DMSOd6) 1.4 (m, 3H), 2.1 (m, 1H), 2.3 (m, 4H), 3.3 (m, 6H), 3.4-3.5 (m, 3H), 3.6 (m, 1H), 4.25 (t, 3H), 5.0 (s, 2H), 6.95 (m, 2H), 7.05-7.15 (m, 2H), 7.2 (s, 1H), 7.3 (m, 2H), 8.1 (d, 1H), 10.8 (s, 1H); MS 422.

20

The starting material was prepared from methyl 2-(4-benzoyloxyphenyl)-2-methyl-4-oxobutanoate as highlighted in example 6 using steps i), ii) and iii), except that 4-chloromethyl-2-methylquinoline was replaced with 2,5-dimethylbenzyl chloride in step i).

EXAMPLE 9**5-[(3-{4-[(3,5-difluorobenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione**

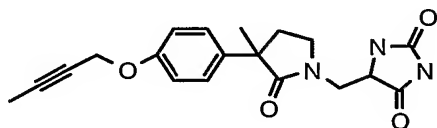
5

An analogous method to that described in Example 6 was used to give 5-[(3-{4-[(3,5-difluorobenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]imidazolidine-2,4-dione 60mg, 0.14mmol; NMR (DMSOd6) 1.35 (d, 2H), 2.1 (m, 1H), 2.2 (m, 2H), 3.2-3.7 (m, 4H), 4.2 (m, 1H), 5.1 (s, 2H), 6.95 (m, 2H), 7.2 (m, 3H) 7.3 (s, 2H), 8.1 (d, 1H) 10.7 (s, 1H); MS

10 430.

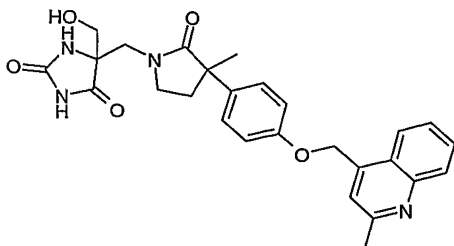
The starting material was prepared from methyl 2-(4-benzyloxyphenyl)-2-methyl-4-oxobutanoate as highlighted in example 6 using steps i), ii) and iii), except that 4-chloromethyl-2-methylquinoline was replaced with 3,5-difluorobenzyl chloride in step i).

15

EXAMPLE 10**5-({3-[4-(but-2-yn-1-yloxy)phenyl]-3-methyl-2-oxopyrrolidin-1-yl}methyl)imidazolidine-2,4-dione**

20 An analogous method to that described in Example 6 was used to give 5-({3-[4-(but-2-yn-1-yloxy)phenyl]-3-methyl-2-oxopyrrolidin-1-yl}methyl)imidazolidine-2,4-dione (52mg, 0.15mmol); NMR (DMSOd6) 1.4 (m, 3H), 1.8 (s, 3H), 2.1 (m, 1H), 2.3 (m, 1H), 3.2-3.7 (m, 4H), 4.25 (s, 1H), 4.7 (s, 2H), 6.9 (m, 2H), 7.3 (m, 2H), 8.0 (d, 1H), 10.7 (s, 1H); MS 365.

25 The starting material was prepared from methyl 2-(4-benzyloxyphenyl)-2-methyl-4-oxobutanoate as highlighted in Example 6 using steps i), ii) and iii), except that 4-chloromethyl-2-methylquinoline was replaced with 1-chlorobut-2-yne in step i).

EXAMPLE 11**5-Hydroxymethyl-5-{3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]-2-oxopyrrolidin-1-ylmethyl}imidazolidine-2,4-dione**

5

To a stirred solution 1-(3-hydroxy-2-oxopropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (106mg, 0.25mmol) in EtOH (1ml) and water (1ml) was added ammonium carbonate (144mg, 1.5mmol) and potassium cyanide (32mg, 0.49mmol). The mixture was heated to 56°C for 90 min. Silica gel (1g) was added and the suspension
10 evaporated. The resultant powder was applied to the top of a 5g bond elute and chromatographed (Flashmaster II, eluent 0-10% EtOH in DCM) to give product as a 1:1 mixture of diastereoisomers (60mg, 0.12 mmol); MS: 489.

The starting material 1-(3-hydroxy-2-oxopropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one was prepared as follows:

15

i) To a solution of 1-(2,3-dihydroxypropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (1.24g, 2.95mmol) (example 6 step ii)) in DCM (30ml) was added imidazole (300mg, 4.4mmol) and *tert*-butyldimethylsilyl chloride (490mg, 3.25mmol). The resultant solution was stirred at RT for 3 h. The solvent was evaporated and
20 the oily residue chromatographed (flashmaster II, 40-100% EtOAc in isohexane) to give 1-[3-(*tert*-butyldimethylsilyloxy)-2-hydroxypropyl]-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one as a colourless oil (1.15g, 2.15mmol); MS: 535.

ii) To a solution of 1-[3-(*tert*-butyldimethylsilyloxy)-2-hydroxypropyl]-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (1.15g, 2.15mmol) in DCM (40ml) was
25 added NMO (435mg, 3.22mmol) and 4A molecular sieves (2.0g). The suspension was stirred for 10 min at RT before addition of TPAP (40mg). The reaction mixture was stirred for a further 30 min before pouring onto a 10g silica gel bond elute and eluted with EtOAc (50ml)

to give 1-[3-(*tert*-butyldimethylsilyloxy)-2-oxopropyl]-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (980mg, 1.8mmol); NMR 0.00 (s, 6H), 0.83 (s, 9H), 1.36 (s, 3H), 2.07 (m, 1H), 2.25 (m, 1H), 2.60 (s, 3H), 3.26 (m, 2H), 4.17 (ABq, 2H), 4.28 (s, 2H), 5.52 (s, 2H), 7.02 (d, 2H), 7.29 (d, 2H), 7.49 (s, 1H), 7.51 (m, 1H), 7.67 (m, 1H), 7.90 (d, 1H),
 5 8.03 (d, 1H); MS: 533.

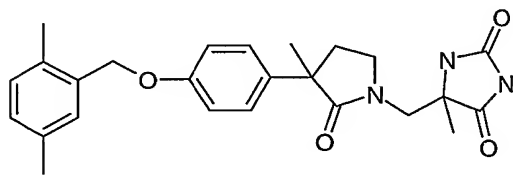
iii) Acetyl chloride (2ml) was added to MeOH (20ml) at 0°C then allowed to warm to RT.

To this was added 1-[3-(*tert*-butyldimethylsilyloxy)-2-oxopropyl]-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one (980mg, 1.8mmol). The reaction mixture was stirred at RT for 10 min and then evaporated to a cream solid. The solid was

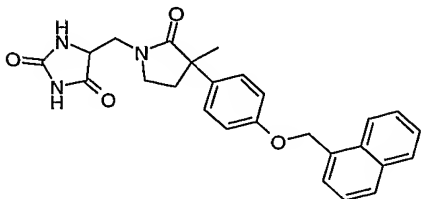
10 dissolved in saturated sodium bicarbonate (50ml) and extracted with DCM (2x50ml). The combined organic phases were dried and evaporated to give 1-(3-hydroxy-2-oxopropyl)-3-methyl-3-[4-(2-methylquinolin-4-ylmethoxy)phenyl]pyrrolidin-2-one as an oil (820mg, 1.96mmol); NMR 1.47 (s, 3H), 2.19 (m, 1H), 2.36 (m, 1H), 2.70 (s, 3H), 3.30 (m, 2H), 4.17 (d, 2H), 4.30 (ABq, 2H), 5.33 (t, 1H), 5.63 (s, 2H), 7.13 (d, 2H), 7.41 (d, 2H), 7.60 (s, 1H),
 15 7.62 (m, 1H), 7.78 (m, 1H), 8.00 (d, 1H), 8.14 (d, 1H); MS: 419.

EXAMPLE 12

5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]-5-methylimidazolidine-2,4-dione



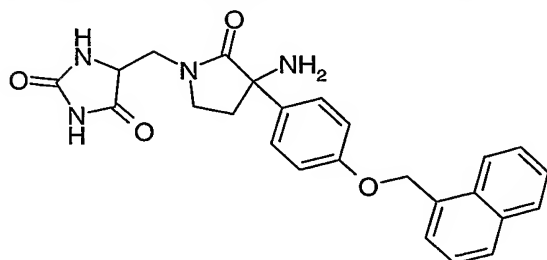
20 An analogous method to that described in Example 3 was used except that 4-chloromethyl-2-methylquinoline was replaced with 2,5-dimethylbenzyl chloride in step i) to afford 5-[(3-{4-[(2,5-dimethylbenzyl)oxy]phenyl}-3-methyl-2-oxopyrrolidin-1-yl)methyl]-5-methylimidazolidine-2,4-dione as a white solid; NMR (DMSO) 1.24 (d, 3H), 1.36 (d, 3H),
 25 2.05 (m, 1H), 2.23 (m, 1H), 2.27 (s, 6H), 3.25 (m, 2H), 3.47 (q, 1H), 4.995 (d, 2H), 6.95 (t, 2H), 7.05 (dd, 1H), 7.10 (d, 1H), 7.22 (d, 1H), 7.265 (dd, 2H), 7.989 (d, 1H), 10.67 (d, 1H); MS: 436 (MH+).

EXAMPLE 13**5-({3-methyl-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-1-yl)methyl}imidazolidine-2,4-dione**

- 5 An analogous method to that described in Example 3 was used to give 5-({3-methyl-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-1-yl)methyl}imidazolidine-2,4-dione as a fawn solid (22mg, 0.05mmol); NMR DMSOd6 2.08 (m, 1H), 2.25 (m, 1H), 3.20-3.66 (m, 4H), 4.25 (d, 1H), 5.50 (s, 2H), 7.00 (d, 2H), 7.29 (d, 2H), 7.43-7.60 (m, 3H), 7.65 (d, 1H), 7.88-8.12 (m, 4H), 7.67 (d, 1H), 10.67 (s, 1H); MS 466(MNa+).

10

The starting material was prepared from 2-(4-benzyloxy-phenyl)-2-methyl-4-oxo-butyric acid methyl ester as highlighted in example 6 using steps i), ii) and iii), except that 4-chloromethyl-2-quinoline was replaced with 1-(chloromethyl)naphthalene.

15 EXAMPLE 14**5-({3-amino-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-1-yl)methyl}imidazolidine-2,4-dione**

- To a stirred solution of *tert*-butyl {1-[(2,5-dioxoimidazolidin-4-yl)methyl]-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-3-yl}carbamate (100mg, 0.18mmol) in DCM (5ml) was added TFA (0.5ml). The reaction was stirred for 90 min, evaporated to dryness and purified by reverse phase HPLC on a Phenomenex C-18 prep column eluting with an acetonitrile:water:TFA gradient, which on further purification on a 10g SCX isolate column gave the product (10 mg, 0.02mmol) as a mixture of diastereoisomers; NMR DMSOd6 2.10-

2.23 (m, 2H), 3.24-3.72 (m, 4H), 4.31 (t, 1H), 5.54 (d, 2H), 7.04 (t, 2H), 7.37 (d, 2H), 7.50-7.61 (m, 3H), 7.67 (d, 1H), 7.93-8.00 (m, 2H), 8.05-8.10 (m, 2H), 10.75 (bs, 1H); MS: 467(MNa⁺).

- 5 The starting material *tert*-butyl {1-[(2,5-dioxoimidazolidin-4-yl)methyl]-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-3-yl} carbamate was prepared as follows:
- i) To a solution of methyl 2-(4-benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-4-oxobutanoate (1.64g, 3.97mmol) (example 4) in 1,2-dichloroethane (23ml) was added 2,2-dimethyl-1,3-dioxolan-4-methylamine (0.52ml, 4.01mmol). The resultant solution was stirred
- 10 at RT for 60 min before addition of sodium triacetoxyborohydride (1.86g, 8.78mmol). The reaction mixture was stirred for a further 1 h and stood at RT for 2 days before addition of DCM (25ml) and brine (25ml). The organic phase was washed with saturated sodium bicarbonate solution (25ml), dried (Na₂SO₄) and evaporated to give an oil. The product was purified by flash chromatography on silica gel (isohexane:ether,50:50) to give *tert*-butyl {3-
- 15 [4-(benzyloxy)phenyl]-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-oxopyrrolidin-3-yl} carbamate as a mixture of diastereoisomers (1.21g, 2.44mmol); NMR DMSO-d₆ 1.24 (s, 6H), 1.33 (s, 9H), 2.77 (d, 2H), 3.33-3.64 (m, 6H), 3.92 (m, 1H), 4.14 (m, 1H), 4.98 (s, 2H), 5.46 (s, 1H), 6.86 (d, 2H), 7.22-7.37 (m, 7H).
- ii) A solution of *tert*-butyl {3-[4-(benzyloxy)phenyl]-1-[(2,2-dimethyl-1,3-dioxolan-4-
- 20 yl)methyl]-2-oxopyrrolidin-3-yl} carbamate (1.20g, 2.42mmol) in (THF:2N HCl, 50ml) was stirred at RT for 2 d, evaporated to near dryness and treated with water (25ml) and saturated aqueous sodium carbonate added to pH8. The reaction mixture was extracted with DCM, dried (MgSO₄) and evaporated. The crude was purified by flash chromatography (20g isolate silica column, eluent 0%→10% MeOH in DCM) to give 3-amino-3-[4-(benzyloxy)phenyl]-1-
- 25 (2,3-dihydroxypropyl)pyrrolidin-2-one as a mixture of diastereoisomers (0.4g, 1.12mmol); MS: 340 (MNH₃⁺).
- iii) To a stirred and cooled (ice/water) mixture of 3-amino-3-[4-(benzyloxy)phenyl]-1-(2,3-dihydroxypropyl)pyrrolidin-2-one (0.4g, 1.12mmol), THF (5ml), water (5ml) and di-*tert*-butyl dicarbonate (0.27g, 1.24mmol) was added potassium carbonate (0.3g, 2.17mmol)
- 30 portionwise. The reaction mixture was stirred at RT overnight, evaporated, extracted with DCM, dried (MgSO₄) and evaporated to dryness to give *tert*-butyl [3-[4-(benzyloxy)phenyl]-

-58-

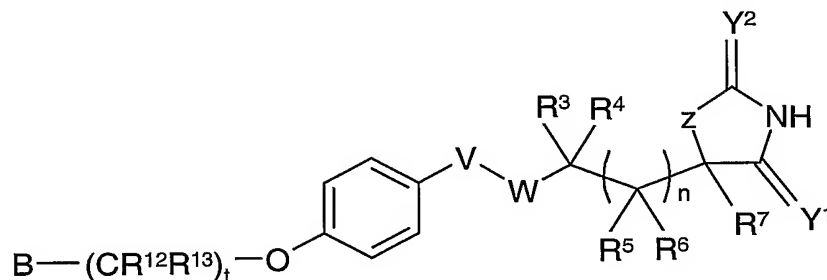
1-(2,3-dihydroxypropyl)-2-oxopyrrolidin-3-yl]carbamate as a mixture of diastereoisomers (0.57g, 1.25mmol) which was used directly in the next step.

- iv) A mixture of *tert*-butyl [3-[4-(benzyloxy)phenyl]-1-(2,3-dihydroxypropyl)-2-oxopyrrolidin-3-yl]carbamate (0.57g, 1.25mmol), cyclohexene (1.27ml, 12.5mmol), EtOH (10ml) and 10% palladium on charcoal was stirred and refluxed for 2 h and then left for 18 h at RT. The reaction mixture was filtered through celite, loaded onto a 20g flash silica isolate column, eluted with DCM, ether, EtOAc and 1/9 MeOH/DCM to give *tert*-butyl [1-(2,3-dihydroxypropyl)-3-(4-hydroxyphenyl)-2-oxopyrrolidin-3-yl]carbamate as a mixture of diastereoisomers (300mg, 0.82mmol); NMR CDCl₃ 1.41 (s, 9H), 2.70 (m, 1H), 2.89 (m, 1H), 3.3-3.6 (m, 6H), 3.8-3.98 (m, 1H), 5.43 (d, 1H), 6.72 (d, 2H), 7.27 (d, 2H); MS: 389 (MNa⁺).
- v) A mixture of *tert*-butyl [1-(2,3-dihydroxypropyl)-3-(4-hydroxyphenyl)-2-oxopyrrolidin-3-yl]carbamate (150mg, 0.41mmol), DMSO (2ml), caesium carbonate (0.266g, 0.82mmol), tetrabutyl ammonium iodide (0.151g, 0.409mmol) and 1-chloromethylnaphthalene (61μl, 0.407mmol) was stirred and heated at 60°C for 90 min. After cooling, EtOAc (25ml) was added and the reaction mixture washed with brine, dried (MgSO₄) and evaporated. The crude product was purified by chromatography (10 silica isolate column, eluant 0%→7% MeOH/DCM) to give *tert*-butyl {1-(2,3-dihydroxypropyl)-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-3-yl}carbamate as a mixture of diastereoisomers (0.14g, 0.28mmol); MS: 529 (MNa⁺).
- vi) To a solution of *tert*-butyl {1-(2,3-dihydroxypropyl)-3-[4-(1-naphthylmethoxy)phenyl]-2-oxopyrrolidin-3-yl}carbamate (140mg, 0.28mmol) in DCM (1.0ml), MeOH (3.5ml) and water (0.7ml) was added sodium periodate (59mg, 0.276mmol). The reaction mixture was stirred for 90 min, evaporated, water (10ml) and EtOAc (10ml) added and stirred for a further 30 min. The organic layer was dried (MgSO₄) and evaporated to yield *tert*-butyl [3-[4-(1-naphthylmethoxy)phenyl]-2-oxo-1-(2-oxoethyl)pyrrolidin-3-yl]carbamate (90mg, 0.19mmol); MS: 529 (M/Hemi acetal/Na⁺).
- vii) To a solution of *tert*-butyl [3-[4-(1-naphthylmethoxy)phenyl]-2-oxo-1-(2-oxoethyl)pyrrolidin-3-yl]carbamate (110mg, 0.316mmol) in EtOH (2.5ml) and water (2.5ml) was added ammonium carbonate (182mg, 1.89mmol) and potassium cyanide (41mg, 0.63mmol). The reaction mixture was stirred and heated at 60 °C for 2 h, left for 2 d at RT, then evaporated to dryness. The resultant residue was dissolved in DCM, filtered and evaporated to give the product as a gum (100mg, 0.84mmol); MS: 576 (MNa⁺), 543 (M⁻).

CLAIMS

We claim:

1. A compound of formula (1) or a pharmaceutically acceptable salt thereof wherein:



formula (1)

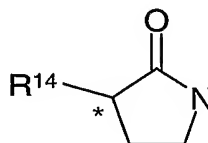
Y^1 and Y^2 are both O;

z is NR^8 , O or S;

n is 0 or 1;

W is CR^1R^2 or a bond;

- 10 V is a group of formula (A):



formula (A)

where the group of formula (A) is bonded through nitrogen to W of formula (1) and through carbon * to phenyl of formula (1);

- 15 t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4} alkyl (optionally substituted by R^9 or C_{1-4} alkoxy or one or more halo), C_{2-4} alkenyl (optionally substituted by halo or R^9), C_{2-4} alkynyl (optionally substituted by halo or R^9), C_{3-6} cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6} cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4} alkyl), heteroaryl (optionally substituted by halo or C_{1-4} alkyl), heterocyclyl (optionally substituted by C_{1-4} alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4} alkenyl or C_2 .

-60-

alkynyl, each being optionally substituted by a group selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, -CONHR⁹, -CONR⁹R¹⁰, -SO₂R¹¹, -SO₂NR⁹R¹⁰, -NR⁹SO₂R¹¹, C₁₋₄alkyl and C₁₋₄alkoxy;

5 **R¹** and **R²** are independently hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl and C₅₋₆cycloalkenyl which group may be optionally substituted by halo, cyano, hydroxy or C₁₋₄alkoxy;

R³, **R⁴**, **R⁵** and **R⁶** are independently hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, aryl, heteroaryl and heterocyclyl which group is
 10 optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₃₋₆cycloalkyl (optionally substituted by one or more R¹⁷), aryl (optionally substituted by one or more R¹⁷), heteroaryl (optionally substituted by one or more R¹⁷), heterocyclyl, -OR¹⁸, -SR¹⁹, -SOR¹⁹, -SO₂R¹⁹, -COR¹⁹, -CO₂R¹⁸, -CONR¹⁸R²⁰, -NR¹⁶COR¹⁸, -SO₂NR¹⁸R²⁰ and -NR¹⁶SO₂R¹⁹;

15 or **R¹** and **R³** together with the carbon atoms to which they are attached form a saturated 3- to 7-membered ring optionally containing 1 or 2 heteroatoms groups selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or nitrogen by C₁₋₄alkyl, -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl;

or **R³** and **R⁴** together with the carbon atom to which they are attached form a saturated 3- to
 20 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or nitrogen by C₁₋₄alkyl, -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl;

or **R³** and **R⁵** together with the carbon atoms to which they are attached form a saturated 3- to
 25 SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or nitrogen by C₁₋₄alkyl, -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl;

or **R⁵** and **R⁶** together with the carbon atom to which they are attached form a saturated 3- to
 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy
 30 and/or nitrogen by C₁₋₄alkyl, -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl;

R⁷ is hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, heteroalkyl, C₃₋₇cycloalkyl, aryl, heteroaryl or heterocyclyl which group is optionally substituted by halo, C₁₋

- alkyl, C₁₋₄alkoxy, C₃₋₇cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and wherein the group from which R⁷ may be selected is optionally substituted on the group and/or on its optional substituent by one or more substituents independently selected from halo, cyano, C₁₋₄alkyl, nitro, haloC₁₋₄alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC₁₋₄alkyl, C₃₋₇cycloalkyl, heterocyclyl, C₁₋₄alkoxyC₁₋₄alkyl, haloC₁₋₄alkoxyC₁₋₄alkyl, -COC₁₋₄alkyl, -OR²¹, -CO₂R²¹, -SR²⁵, -SOR²⁵, -SO₂R²⁵, -NR²¹COR²², -CONR²¹R²² and -NHCONR²¹R²²;
- 5 or R³ and R⁷ together with the carbon atoms to which they are each attached and (CR⁵R⁶)_n form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO₂ where the ring is optionally substituted on carbon by C₁₋₄alkyl, fluoro or C₁₋₃alkoxy and/or nitrogen by C₁₋₄alkyl, -COC₁₋₃alkyl or -SO₂C₁₋₃alkyl;
- 10 R⁸ is hydrogen or methyl;
- R⁹ and R¹⁰ are independently hydrogen, C₁₋₆alkyl or C₃₋₆cycloalkyl;
- or R⁹ and R¹⁰ together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring;
- 15 R¹¹ is C₁₋₆alkyl or C₃₋₆cycloalkyl;
- R¹² and R¹³ are independently selected from hydrogen, C₁₋₆alkyl and C₃₋₆cycloalkyl;
- R¹⁴ is hydrogen, nitrile, -NR²³R²⁴ or C₁₋₄alkyl (optionally substituted by halo, -OR²³ and -NR²³R²⁴);
- R¹⁶, R²³ and R²⁴ are independently hydrogen or C₁₋₆alkyl;
- 20 R¹⁷ is selected from halo, C₁₋₆alkyl, C₃₋₆cycloalkyl and C₁₋₆alkoxy;
- R¹⁸ is hydrogen or a group selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC₁₋₄alkyl and heteroarylC₁₋₄alkyl which group is optionally substituted by one or more halo;
- R¹⁹ and R²⁵ are independently a group selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₅₋₆cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC₁₋₄alkyl and heteroarylC₁₋₄alkyl which group is optionally substituted by one or more halo;
- 25 R²⁰ is hydrogen, C₁₋₆alkyl or C₃₋₆cycloalkyl;
- or R¹⁸ and R²⁰ together with the nitrogen to which they are attached form a heterocyclic 4- to 7- membered ring;
- 30 R²¹ and R²² are independently hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, aryl and arylC₁₋₄alkyl.

2. A compound according to claim 1 wherein B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkyl (optionally substituted by one or more halo), C₂₋₄alkynyl, heteroaryl, -OR⁹, cyano, -NR⁹R¹⁰, -
5 CONR⁹R¹⁰ and -NR⁹COR¹⁰; or B is C₂₋₄alkenyl or C₂₋₄alkynyl optionally substituted by C₁₋₄alkyl, C₃₋₆cycloalkyl or heterocyclyl.
3. A compound according to claim 1 wherein B is phenyl, naphthyl, pyridyl, quinoliny, isoquinoliny, thienopyridyl, 1,8-naphthyridinyl, 2,3-methylenedioxyphenyl, 3,4-
10 methylenedioxyphenyl, 1,6-naphthyridinyl, thienopyrimidinyl, pyridoimidazolyl, benzimidazolyl, benzofuranyl, benzothienyl, indolyl, benzothiazolyl, benzotriazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, indoliziny, isobenzofuranyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, indoliny, tetrahydroquinoliny, tetrahydroisoquinoliny or isoindoliny, where each is optionally substituted by one or more groups independently
15 selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C₁₋₄alkyl (optionally substituted by one or more fluoro), C₂₋₄alkynyl, heteroaryl, -OR⁹, cyano, -NR⁹R¹⁰, -CONR⁹R¹⁰ and -NR⁹COR¹⁰; or B is vinyl or ethynyl optionally substituted by C₁₋₄alkyl.
4. A compound according to claim 2 wherein B is aryl, heteroaryl or C₂₋₄alkynyl
20 optionally substituted by halo or C₁₋₄alkyl.
5. A compound according to claim 4 wherein B is 2-methylquinolin-4-yl or 2,5-dimethylphenyl.
- 25 6. A compound according to any one of the preceding claims wherein t is 1.
7. A compound according to any one of the preceding claims wherein R⁷ is selected from hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, hydroxyC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl and aryl.
- 30 8. A compound according to any one of the preceding claims wherein R¹⁴ is hydrogen, methyl or amino.

9. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically-acceptable diluent or carrier.

10. A compound according to claim 1 for use as a medicament.

5

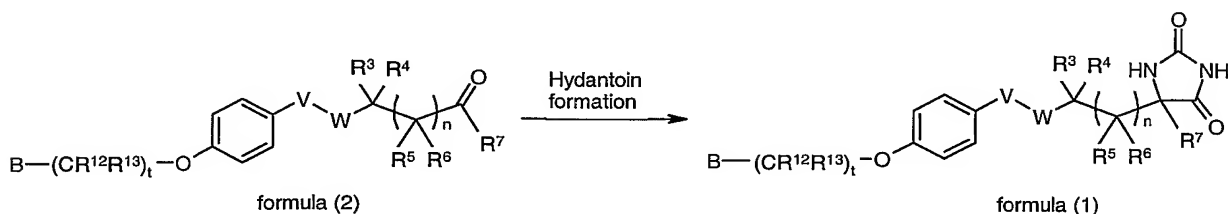
11. The use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man.

10

12. A method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound according to claim 1.

15

13. A process for preparing a compound according to claim 1, comprising the steps of converting a ketone or aldehyde of formula (2) into a compound of formula (1);



and thereafter if necessary:

- 20 i) converting a compound of formula (1) into another compound of formula (1);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/03914

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 A61K31/47 A61P43/00 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 429 213 B1 (CHU-BIAO XUE ET AL.) 6 August 2002 (2002-08-06) * column 3, 84-86 *	1,9,11
A	US 6 340 691 B1 (JEREMY I. LEVIN ET AL.) 22 January 2002 (2002-01-22) column 5; claims	1,9,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

28 January 2004

Date of mailing of the international search report

09/02/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/03914

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/03914

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6429213	B1	06-08-2002	US 2003139597 A1	24-07-2003
			AU 4692399 A	05-01-2000
			CA 2333554 A1	23-12-1999
			EP 1087937 A1	04-04-2001
			JP 2002518368 T	25-06-2002
			WO 9965867 A1	23-12-1999
US 6340691	B1	22-01-2002	US 2002147342 A1	10-10-2002